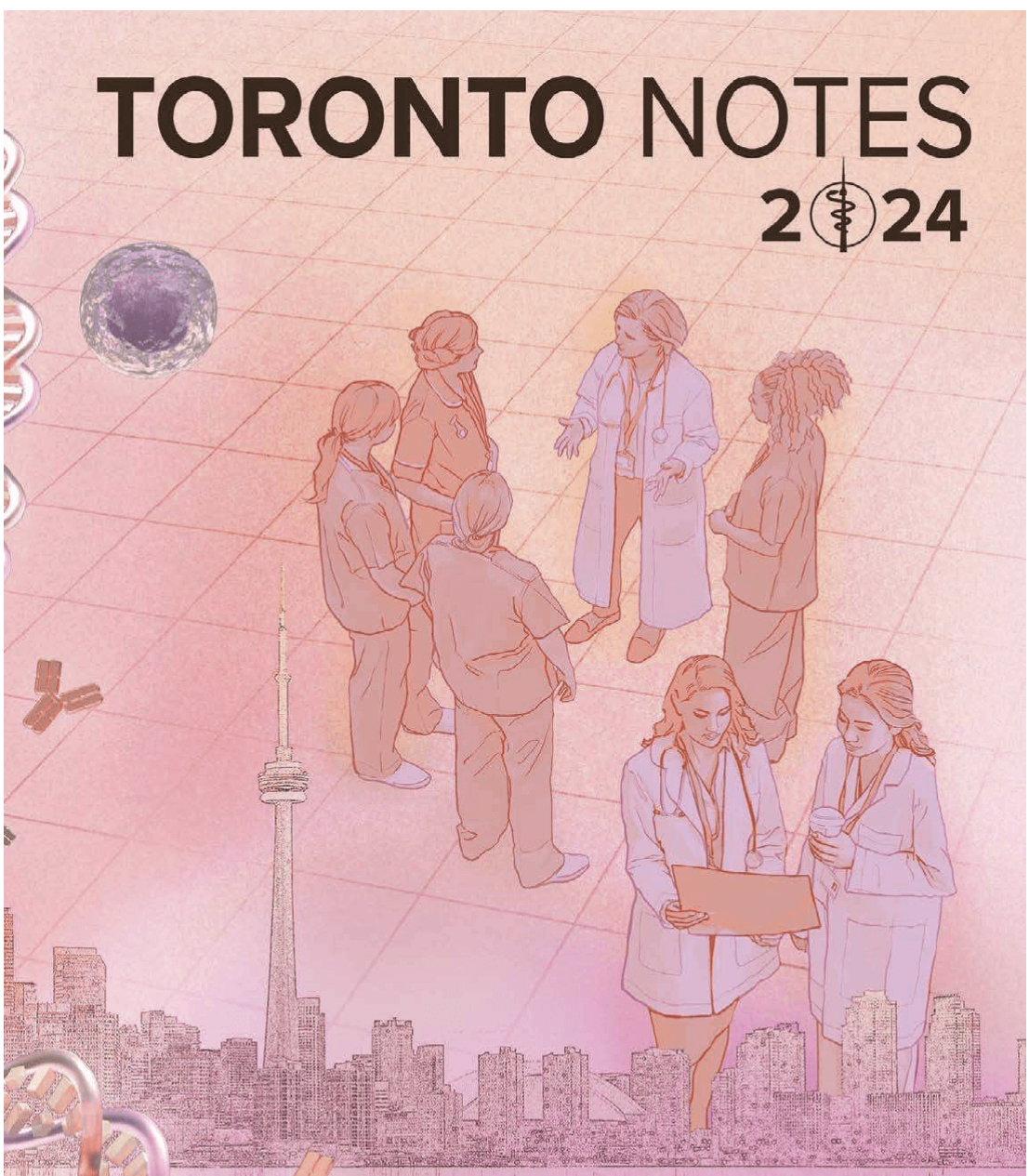
TORONTO NOTES

2024



COMPREHENSIVE MEDICAL REFERENCE
AND A REVIEW FOR MCCQE

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2024

Comprehensive Medical Reference
and a Review for the Medical Council of Canada Qualifying Exam
(MCCQE)

40th Edition

Editors-in-Chief:
Melissa Galati and Yasmin Motekalem

Toronto Notes for Medical Students, Inc.
Toronto, Ontario, Canada

Fortieth Edition

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Typeset and production by Type & Graphics Inc.
ISBN 978-1-998874-08-8 (40th ed.)

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Cover illustration: Amy Jiao and Vadym Lytvynov
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Library of Congress Cataloging-in-Publication Data is available upon request

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Note:

Many of you have wondered about the *Toronto Notes* logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius' healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

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Preface – From the Editors

Dear Readers,

We are grateful to present *Toronto Notes 2024* to you. This edition is the product of an exceptional effort from the hundreds of editors and contributors who worked tirelessly with us as we navigated through the year. Together, we have created this milestone 40th edition of Toronto Notes, thus continuing our organization's rich tradition of providing an up-to-date, comprehensive, and concisely written medical resource to our readers.

Forty years ago, *Toronto Notes* began as a humble initiative, with medical students from the University of Toronto collecting and circulating their notes. Four decades later – with annual editions and an ever-expanding vision – *Toronto Notes* has become one of the most trusted medical review texts; it is a resource that is cherished by trainees and physicians throughout Canada and around the world.

The Toronto Notes for Medical Students Inc. is a nonprofit corporation whose mission is to provide a trusted medical resource in order to give back to our community. Keeping in line with our values and community needs, all proceeds from *Toronto Notes* sales are directly donated to support both global and local initiatives. Among other initiatives, we have supported U of T Medicine class activities, student scholarships and bursaries, *Daffdydil*, U of T's annual musical fundraiser for the Canadian Cancer Society, and the entirety of our (over twenty-five) student-led outreach programs that seek to enrich lives in the community, including the *Indigenous Student Mentorship Fund* and the *Black Medical Students' Association of Canada*.

This is why we, and all the members of our U of T team, gladly dedicated so many hours toward this immensely involved project. As our valued reader, we thank you for your honest and vital financial contribution through your purchase of our textbook. Each book sold makes an important difference.

The 2024 edition features substantial content revisions to the text, figures, and graphics of all 32 chapters, following a comprehensive review by our student and faculty editorial team. Up-to-date, evidence-based medicine studies are also summarized in highlighted boxes throughout the text. Once again, our *Ethical, Legal, and Organizational Medicine* chapter has been thoroughly revised, and all chapters reflect the most-updated COVID-19 guidelines. Our editors have also approached each chapter with the new MCCQE objectives on providing anti-oppressive health care, and quality improvement and patient safety in mind. In addition to content updates, the *Toronto Notes 2024 Clinical Handbook* has been restructured, and pared down to prioritize high-yield content and Do Not Miss Diagnoses to guide your learning during clerkship rotations.

We sincerely thank each of our 215 student editors and 97 faculty editors, whose meticulous revisions and shared dedication to the bettering of this text has helped make *Toronto Notes 2024* possible. We have learned so much from leading this team, and are especially grateful to everyone for contributing to *Toronto Notes* even with challenging time commitments and demands. We thank our incredible Associate Editors – Karolina Gaebe, Lyra Halili, Alyssa Li, Huaqi Li, Michelle Lim, Saba Manzoor, Vrati M. Mehra, Farah Qaiser, and Dorrin Zarrin Khat – for their tireless leadership, exceptional organization, and wonderful teamwork. The success of this edition would not be possible without their efforts and we are exceedingly grateful to have worked with them. We also thank our Clinical Handbook Editors – Hardil Bhatt, David Buchan, Mercy Danquah, Rajiv Tanwani, and Timothy Zhang – for their exceptional editorial leadership towards spearheading the work on the 2024 edition. We owe a great deal of gratitude to the Editors-in-Chief of the 2023 edition – Anders Erickson and Jennifer Parker– for their guidance over the past year. We would also like to thank the wonderful BMC illustration team for their work, notably Amy Jiao and Vadym Lytvynov who worked iteratively to embrace the spirit of Toronto Notes through their cover design. Lastly, we thank our longtime partners at Type & Graphics Inc – especially our backbone, Enrica Aguilera and Maria Garcia — for their years of support and excellent work producing *Toronto Notes 2024*. Finally, we thank you for supporting our initiative by purchasing and reading our product. We hope that you will find *Toronto Notes 2024* to be a useful companion on your medical journey, both now and for years to come.

Sincerely,

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Acknowledgements

We would like to acknowledge the exceptional work of all previous Toronto Notes (formerly MCCQE Notes) Editors-in-Chief and their editorial teams. The 40th edition of this text was made possible with their contributions.

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How To Use This Book

This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of *Toronto Notes* allows easy identification of important information.
These items are indicated by icons interspersed throughout the text:

Icon	Icon Name	Significance
	Key Objectives	This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics.
	Clinical Pearl	This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text.
	Memory Aid	This icon is found in sidebars of the text. It identifies helpful mnemonic devices and other memory aids.
	Clinical Flag	This icon is found in sidebars of the text. It indicates information or findings that require urgent management or specialist referral.
	Evidence Based Medicine	This icon is found in sidebars of the text. It identifies key research studies for evidence-based clinical decision making related to topics discussed in the accompanying text.
	Colour Photo Atlas	This icon is found next to headings in the text. It indicates topics that correspond with images found in the Colour Photo Atlas available online (www.torontonotes.ca).
	Radiology Atlas	This icon is found next to headings in the text. It indicates topics that correspond to images found in the Radiology Atlas available online (www.torontonotes.ca).
	Online Resources	This icon is found next to headings in the text. It indicates topics that correspond with electronic resources such as Functional Neuroanatomy or ECGs Made Simple, available online (www.torontonotes.ca).

Chapter Divisions

To aid in studying and finding relevant material quickly, many chapters incorporate the following general framework:

Basic Anatomy/Physiology Review
- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

Common Differential Diagnoses
- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

Diagnoses
- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

Common Medications
- a quick reference section for review of medications commonly prescribed

Common Acronyms and Abbreviations Used in Medicine

The following are common medical acronyms/abbreviations that may be used without definition throughout the Toronto Notes text. These are typically not included in the acronym list at the beginning of each chapter. Please refer back to this list for definitions.

[ ]	concentration
β-hCG	beta human chorionic gonadotropin
ABx	antibiotics
ACE	angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	absolute risk
ASA	acetylsalicylic acid
AST	aspartate transaminase
aSx	asymptomatic
AXR	abdominal x-ray
BID	twice a day (bis in die)
BMI	body mass index
BP	blood pressure
BPM/bpm	beats per minute
C/I	contraindication
C&S	culture and sensitivity
CAD	coronary artery disease
CBC	complete blood count
CC	chief complaint
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
Cr	creatinine
CRH	corticotropin-releasing hormone
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
D&C	dilatation and curettage
dBP	diastolic blood pressure
DDx	differential diagnosis
DM	diabetes mellitus
DNR	do not resuscitate
Dx	diagnosis
ECG	electrocardiogram
ED	emergency department
EEG	electroencephalography
EMG	electromyography
ENT	ears, nose, and throat
ESR	erythrocyte sedimentation rate
EtOH	ethanol/alcohol
FMHx	family medical history
FSH	follicle stimulating hormone
G6PD	glucose-6-phosphate dehydrogenase
GGT	gamma-glutamyl transferase
GH	growth hormone
GHB	gamma hydroxybutyrate
GI	gastrointestinal
GU	genitourinary
Hb	hemoglobin
HIV	human immunodeficiency disease
HR	heart rate
HTN	hypertension
Hx	history
I&D	incision and drainage
ICP	intracranial pressure
ICU	intensive care unit
IM	intramuscular
IV	intravenous
JVP	jugular venous pressure
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LR	likelihood ratio

Common Acronyms and Abbreviations Used in Medicine

MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MDI	metered-dose inhaler
MI	myocardial infarction
MRI	magnetic resonance imaging
MSK	musculoskeletal
N/V	nausea/vomiting
NG	nasogastric
NMDA	N-Methyl-D-aspartate
NPO	nothing by mouth (nil per os)
NSAID	non-steroidal anti-inflammatory drug
OR	operating room
OTC	over-the-counter
PCR	polymerase chain reaction
PE	pulmonary embolism
PMHx	past medical history
PO	oral administration (per os)
POCUS	point-of-care ultrasound
PPI	proton pump inhibitor
PRN	as needed (pro re nata)
QID	four times a day (quater in die)
RBC	red blood cell
RCT	randomized controlled trial
ROS	review of symptoms
Rx	medical prescription
sBP	systolic blood pressure
SC	subcutaneous
SL	sublingual
SLE	systemic lupus erythematosus
SOB	shortness of breath
STAT	urgent or immediately (statum)
STI	sexually transmitted infection
Sx	symptom(s)
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TB	tuberculosis
TID	three times a day (ter in die)
TNM	tumour, nodes, and metastases
TRH	thyroid releasing hormone
TSH	thyroid stimulating hormone
Tx	treatment
U/A	urinalysis
U/S	ultrasound
UTI	urinary tract infection
UTox	urine toxicology screen
VDRL	Venereal Disease Research Laboratory test
WBC	white blood cell
wt	weight

Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor
To convert from the SI unit to the conventional unit, **divide** by conversion factor

	Conventional Unit	Conversion Factor	SI Unit
ACTH	pg/mL	0.22	pmol/L
Albumin	g/dL	10	g/L
Bilirubin	mg/dL	17.1	µmol/L
Calcium	mg/dL	0.25	mmol/L
Cholesterol	mg/dL	0.0259	mmol/L
Cortisol	µg/dL	27.59	nmol/L
Creatinine	mg/dL	88.4	µmol/L
Creatinine clearance	mL/min	0.0167	mL/s
Ethanol	mg/dL	0.217	mmol/L
Ferritin	ng/mL	2.247	pmol/L
Glucose	mg/dL	0.0555	mmol/L
HbA1c	%	0.01	proportion of 1.0
Hemaglobin	g/dL	10	g/L
HDL cholesterol	mg/dL	0.0259	mmol/L
Iron, total	µg/dL	0.179	µmol/L
Lactate (lactic acid)	mg/dL	0.111	mmol/L
LDL cholesterol	mg/dL	0.0259	mmol/L
Leukocytes	x 10^3cells/mm ^{3}	1	x 10^9cells/L
Magnesium	mg/dL	0.411	mmol/L
MCV	μm^3	1	fL
Platelets	x 10^3cells/mm ^{3}	1	x 10^9cells/L
Reticulocytes	% of RBCs	0.01	proportion of 1.0
Salicylate	mg/L	0.00724	mmol/L
Testosterone	ng/dL	0.0347	nmol/L
Thyroxine (T_4)	ng/dL	12.87	pmol/L
Total Iron Binding Capacity	µg/dL	0.179	µmol/L
Triiodothyronine (T_3)	pg/dL	0.0154	pmol/L
Triglycerides	mg/dL	0.0113	mmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
Uric acid	mg/dL	59.48	µmol/L

Celsius → Fahrenheit	F = (C x 1.8) + 32
Fahrenheit → Celsius	C = (F – 32) x 0.5555
Kilograms → Pounds	1 kg = 2.2 lbs
Pounds → Ounces	1 lb = 16 oz
Ounces → Grams	1 oz = 28.3 g
Inches → Centimetres	1 in = 2.54 cm

Commonly Measured Laboratory Values

Test	Conventional Units	SI Units
Arterial Blood Gases		
pH	7.35-7.45	7.35-7.45
PCO_2	35-45 mmHg	4.7-6.0 kPa
PO_2	80-105 mmHg	10.6-14 kPa
Serum Electrolytes		
Bicarbonate	22-28 mEq/L	22-28 mmol/L
Calcium	8.4-10.2 mg/dL	2.1-2.5 mmol/L
Chloride	95-106 mEq/L	95-106 mmol/L
Magnesium	1.3-2.1 mEq/L	0.65-1.05 mmol/L
Phosphate	2.7-4.5 mg/dL	0.87-1.45 mmol/L
Potassium	3.5-5.0 mEq/L	3.5-5.0 mmol/L
Sodium	136-145 mEq/L	136-145 mmol/L
Serum Nonelectrolytes		
Albumin	3.5-5.0 g/dL	35-50 g/L
ALP	35-100 U/L	35-100 U/L
ALT	8-20 U/L	8-20 U/L
Amylase	25-125 U/L	25-125 U/L
AST	8-20 U/L	8-20 U/L
Bilirubin (direct)	0-0.3 mg/dL	0-5 µmol/L
Bilirubin (total)	0.1-1.0 mg/dL	2-17 µmol/L
BUN	7-18 mg/dL	2.5-7.1 mmol/L
Cholesterol	<200 mg/dL	<5.2 mmol/L
Creatinine (female)	10-70 U/L	10-70 U/L
Creatinine (male)	25-90 U/L	25-90 U/L
Creatine Kinase – MB fraction	0-12 U/L	0-12 U/L
Ferritin (female)	12-150 ng/mL	12-150 µg/L
Ferritin (male)	15-200 ng/mL	15-200 µg/L
Glucose (fasting)	70-110 mg/dL	3.8-6.1 mmol/L
HbA1c	<6%	<0.06
LDH	100-250 U/L	100-250 U/L
Osmolality	275-300 mOsm/kg	275-300 mOsm/kg
Serum Hormones		
ACTH (0800h)	<60 pg/mL	<13.2 pmol/L
Cortisol (0800h)	5-23 µg/dL	138-635 nmol/L
Prolactin	<20 ng/mL	<20 ng/mL
Testosterone (male, free)	9-30 ng/dL	0.31-1 pmol/L
Thyroxine (T_4)	5-12 ng/dL	64-155 nmol/L
Triiodothyronine (T_3)	115-190 ng/dL	1.8-2.9 nmol/L
TSH	0.5-5 µU/mL	0.5-5 µU/mL
Hematologic Values		
ESR (female)	0-20 mm/h	0-20 mm/h
ESR (male)	0-15 mm/h	0-15 mm/h
Hemoglobin (female)	12.3-15.7 g/dL	123-157 g/L
Hemoglobin (male)	13.5-17.5 g/dL	140-174 g/L
Hematocrit (female)	36-46%	36-46%
Hematocrit (male)	41-53%	41-53%
INR	1.0-1.1	1.0-1.1
Leukocytes	4.5-11 x 10^3cells/mm ^{3}	4.5-11 x 10^9cells/L
MCV	88-100 μm^3	88-100 fL
Platelets	150-400 x $10^3/mm^3$	150-400 x 10^9/L
PTT	25-35 s	25-35 s
Reticulocytes	0.5-1.5% of RBC	20-84 x 10^9/L

ELOM Ethical, Legal, and Organizational Medicine

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Acronyms **ELOM2**

Ethical Issues in Health Care **ELOM2**

The Canadian Healthcare System **ELOM2**
Overview of Canadian Healthcare System
Legal Foundation
History of the Canadian Healthcare System and Crown-Indigenous Relations Pursuant to Healthcare
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Ethical and Legal Issues in Canadian Medicine **ELOM9**
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Conscientious Objection

Clinical Informatics and Ethical Considerations **ELOM25**
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Indigenous Health **ELOM25**
Overview of the History and Impact of Colonialism
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Indigenous Health Coverage and Jurisdictions
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References **ELOM32**

Further information on these topics can be found in the Objectives of the Considerations of the Legal, Ethical, and Organizational Aspects of the Practice of Medicine (CLEO) – which can be downloaded free of charge from the Medical Council of Canada website at http://mcc.ca/wp-content/uploads/CLEO.pdf.

There are three main types of law in Canada: criminal, civil, and administrative. The penalties for violating each are, in general, as follows: criminal – fine or incarceration; civil – monetary damages paid to the wronged party; and administrative – sanctions by the regulator (such as a suspension by the College of Physicians and Surgeons). All three types of law can be engaged by a single act. For example, a physician that inappropriately touches a patient can be liable for criminal (sexual assault), civil (monetary damages paid to the patient for the civil wrong of sexual assault), and administrative (fines and sanctions up to and including loss of ability to practice medicine for sexual abuse) penalties.

Canadian law applicable to medical practice varies between jurisdictions and changes over time.

Criminal law is nationwide, but civil and administrative law varies between provinces and territories. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.

Acronyms

AE	adverse event	CPSO	College of Physicians and Surgeons of Ontario	LMCC	Licentiate of the Medical Council of Canada	PIPEDA	Personal Information Protection and Electronic Documents Act
ART	assisted reproductive technologies	EMR	electronic medical record	MAID	Medical Assistance in Dying	POA	Power of Attorney
CFMS	Canadian Federation of Medical Students	FMEQ	Fédération médicale étudiante du Québec	MCC	Medical Council of Canada	PTMA	Provincial/Territorial Medical Association
CFPC	College of Family Physicians of Canada	FRCPC	Fellow of the Royal College of Physicians of Canada	OECD	Organization for Economic Co-operation and Development	RCPSC	Royal College of Physicians and Surgeons of Canada
CIHR	Canadian Institutes of Health Research	FRCSC	Fellow of the Royal College of Surgeons of Canada	OMA	Ontario Medical Association	RDoC	Resident Doctors of Canada
CMA	Canadian Medical Association	GA	gestational age	OTC	over the counter	SDM	substitute decision-maker
CME	continuing medical education	GDP	gross domestic product	PHO	Provincial House staff Organization	TRC	Truth and Reconciliation Commission
CMPA	Canadian Medical Protective Association	HCCA	Health Care Consent Act	PHIPA	Personal Health Information Protection Act		
		IVF	in vitro fertilization				

The practice of medicine and ethics are inherently linked. As the complexity of medicine evolves, so do the principles that we use to guide ethical decision-making in clinical practice. Traditionally, four fundamental principles: Beneficence, Nonmaleficence, Autonomy, and Justice have been the basis of clinical ethics. In recognition of this complexity and the importance of relationships within the practice of medicine, the CMA Code of Ethics recommends the use of a broader array of ethical principles. Ethical issues are usually identifiable by the presence of a moral dilemma and are navigated by carefully considering all factors involved and selecting the best possible option. Understanding how to navigate ethical dilemmas is extremely important, as they present at all levels of medical training and practice. These dilemmas can be approached by first identifying the ethical issue and then by using ethics frameworks. Having early ethical training allows one to develop the necessary skills to navigate various morally ambiguous scenarios that arise in the practice of medicine. Although medical ethics is an ever-evolving discipline, this chapter seeks to provide an overview of relevant frameworks and a basic guide to knowing how to best act in the face of ethical dilemmas.

Ethical Issues in Health Care

Managing Controversial and Ethical Issues in Practice

- use an Ethics Framework. Many hospitals have adopted the IDEA framework or versions of it.
- determine the ethical issue or question eg. is it ethical to allow patient X to refuse life saving treatment?
- discuss the issue(s) in a manner that is as objective and non-judgmental as possible (separate facts from assumptions that may carry health care provider' bias)
- involve all relevant interprofessional colleagues who are involved in the care of the patient (or the issue if it is an organisational ethics issue)
- consider what hospital, university, regulatory college policies and laws are applicable to the case
- be mindful that everyone involved in the case (patients, family members and healthcare providers) all bring their own values and lived experiences to the issue at hand
- identify if any options are outside of the physician's moral boundaries (e.g. something to which the physician has a conscientious objection) and refer to another physician, if appropriate
- consult with a bioethicist and/or the appropriate ethics committees or boards

IDEA Framework Tool
Identify the facts
Determine the relevant ethical principles
Explore the options
Act on your decision and evaluate

Intentions and Impact Tool
1. What is the intention of an action?
2. What is the impact of an action?

The Canadian Healthcare System

Overview of Canadian Healthcare System

- one federal, three territorial, and ten provincial systems
- major complexities in establishment of Canadian health policy include geographical diversity, socioeconomic divisions, and international pressures
- financed by both the public (70%) and private (30%) sectors
- each provincial/territorial plan must cover all medically necessary health services and remain in compliance with the Canada Health Act in order to receive federal transfers
- provincial/territorial governments may choose to offer and fund supplementary services not covered under the *Canada Health Act*, such as prescription drugs and vision care
- non-insured health services and fees are either covered by private insurance or by the individual
- workers' compensation funds cover treatment for work-related injuries and diseases

Table 1. Division of Government Responsibilities in Healthcare

Federal Government	Provincial Government
Healthcare services for Indigenous peoples (Status First Nations peoples and Inuit only, Non-Insured Health Benefits (NIHB)), federal government employees (RCMP and armed forces), immigrants, and civil aviation personnel	Establishment, maintenance, and management of hospitals, asylums, charities, and charitable institutions (*Constitution Act*, 1867)
Marine hospitals and quarantine (Constitution Act, 1867)	Licensing of physicians, nurses, and other health professionals
Investigations into public health	Determining the standards for licensing all hospitals
Regulation of food and drugs	Administering provincial medical insurance plans
Inspection of medical devices	Financing healthcare facilities
Administration of healthcare insurance	Delivery of certain public health services
General information services related to health conditions and practices	
Role in health derives from constitutional responsibility over criminal law, spending powers, and legislation for 'peace, order, and good government.' Examples include *Canada Health Act, Food and Drugs Act, Controlled Substances Act*, and *Canada Health Transfer Act*)	

Principles of the Canada Health Act

1. Public Administration: provincial/territorial health insurance programs must be administered on a not-for-profit basis by public authorities
2. Comprehensiveness: provincial/territorial health insurance programs must cover all medically necessary diagnostic, physician, and hospital services
3. Universality: all eligible residents must be entitled to healthcare services (including status First Nations peoples and Inuit; note that non-status First Nations and Métis are included under all eligible residents)
4. Portability: emergency health services must be available to Canadians who are outside their home province, paid for by the home province
5. Accessibility: provincial/territorial plans must ensure reasonable access to medically necessary hospital and physician services without financial or other barriers

The federal government can reduce its contributions to provinces that violate the key principles of the *Canada Health Act*

Legal Foundation

- the legal foundation of the Canadian health system is based on:
  - five constitutional documents:
    1. Royal Proclamation (1763): the foundation for the rights of Indigenous peoples in Canada; sets out the sovereignty of Indigenous peoples in Canada
    2. *Constitution Act* (1867): deals primarily with the jurisdictional power between federal and provincial governments
    3. Treaty 6 (1876): included the Medicine Chest Clause, which addresses Indigenous sovereignty in healthcare delivery and equitable access to all forms of medicine
    4. Dreaver vs. King court ruling (1935): provided the legal precedence for Non-Insured Health Benefits
    5. The Canadian Charter of Rights and Freedoms (1982): does not guarantee a right to healthcare; but, if the government decides to finance healthcare, they are constitutionally obliged to do so consistently with the rights and freedoms outlined in the Charter (including the right to equality, physicians' mobility rights, etc.)
  - two statutes:
    1. *Canada Health Act* (1984): outlines the national terms and conditions that provincial health systems must meet in order to receive federal transfer payments
    2. *Canada Health and Social Transfer Act* (1996): federal government gives provinces a single grant for healthcare, social programs, and post-secondary education; division of resources at provinces' discretion

History of the Canadian Healthcare System and Crown-Indigenous Relations Pursuant to Healthcare

1534 Europeans first arrive in Canada
- settlers find healthy inhabitants with complex societies, cultures, and belief systems
- Indigenous peoples' have specific knowledge of local environment and medicines
  - early instance of medical practice occurs when local Indigenous nation (Haudenosaunee) used cedar as a source of vitamin C to treat scurvy experienced by European settlers

1763 *Royal Proclamation*
- identifies Indian Country that was under British sovereignty but Indigenous possession
- sets out guidelines for European settlement of Indigenous territories in what is now North America; statements include: Aboriginal title (a legal term for ancestral land rights) has existed and continues to exist, and that all land would be considered Aboriginal land unless ceded by treaty
  - forbids settlers from claiming land from the Indigenous occupants, unless it was first bought by the Crown and then sold to the settlers
  - only the Crown can buy land from First Nations

1764 *Treaty of Niagara*
- the treaty is signed with 24 Indigenous Nations represented
- Indigenous peoples and the Crown agree to co-exist and build their relationship on Turtle Island

1867 *British North America Act* (now *Constitution Act* 1867)
- establishes Canada as a confederacy
- "establishment, maintenance, and management of hospitals" under provincial jurisdiction
- gives the federal government control over lands reserved for "Indians"

1870 *Manitoba Act*
- Métis land is protected and they are given an additional 1.4 million acres for their descendants
- this act was subsequently ignored and infringed upon as this land was given freely to incoming settlers

1871-1921 *Numbered Treaties*
- transfer large tracts of Indigenous land to the Crown with various promises made to Indigenous Peoples
- Treaty 6 explicitly includes medicine, while others contain agreements related to social factors affecting health

1876 *Indian Act*
- reinforces the federal government's exclusive jurisdiction over Indians and lands reserved for Indians
- gives complete control of "Indian bands," status, and reserves to the Canadian government
- enfranchisement (the process of terminating one's legal Indian Status, identity, and ancestral rights in order to gain full Canadian citizenship) becomes legally compulsory in many situations (such as becoming a physician)
- denies women equal citizenship status
- denies the right to vote
- outlaws the practice of Indigenous culture and spirituality
- imposes band councils and "Indian agents"
- restricts First Nations peoples from leaving reserves without the Indian agent's permission

1884-1996 Residential Schools and Indian Hospitals
- legislated genocide (see Public Health and Preventive Medicine, PH5)

1885 Execution of Métis leader Louis Riel
- leader of the North-West Rebellion against the Federal government due to infringement on Métis ancestral lands, rights, and way of life

1939 Court Decision *Reference Re Eskimo* rules that the federal government has similar responsibility for Inuit people as Indigenous Peoples
- following this decision the government developed policies that enforced assimilation and benefited governmental goals, with disregard for Inuit wellbeing. This leads to extensive harm, some of which are noted below:
  - coercive relocation to isolated and sedentary communities away from ancestral lands, ending seasonally dynamic way of life
  - sled dogs were killed, which discontinued the Inuit traditional way of life and forced them to rely on government supplies
  - discs, to be worn around the neck, were issued with numbers in lieu of Inuit surnames and to ease bureaucratic workload

1965 *Royal Commission on Health Services* (Hall Commission) recommends federal leadership and financial support with provincial government operation

1966 *National Medical Care Insurance Act*
- federal government's first legislation with the goal of free access to healthcare
- federal government to pay half of medicare costs in any province with insurance plans that meet criteria of being universal, publicly administered, portable, and comprehensive
- Indian Health Services budget is reduced under the guise of equality and social and legal integration. Individuals can only receive support for healthcare services if they prove they are Indigenous, have been refused funds from their band, and can not obtain provincial health services. Financial limits are set to prevent "overuse" of services. This creates further barriers to accessing healthcare, while reducing barriers for non-Indigenous peoples

1984 *Canada Health Act* is passed by federal government
- replaces *Medical Care Act* (1966) and *Hospital Insurance and Diagnostic Services Act* (1957)
- provides federal funds to provinces with universal hospital insurance
- maintains federal government contribution at 50% on average, with poorer provinces receiving more funds

- medical insurance must be "comprehensive, portable, universal, and publicly administered"
- bans extra-billing by new fifth criterion: accessibility

1985 *Bill C-31*
- the *Indian Act* forced Indigenous women who married non-Indigenous men to lose their Indian status
- *Bill C-31* attempted to stop the involuntary enfranchisement of Indigenous women (and their children) who married non-Indigenous men
- *Bill C-31* in 2011 and later cases ensured that eligible grandchildren of women who lost status could regain it

1990 Oka Crisis
- land dispute over ancestral Kanienkehaka (Mohawk) territory
- brought about the Royal Commission on Aboriginal Peoples (1996)

1996 *Canada Health and Social Transfer Act* passed by federal government
- federal government gives provinces a single grant for healthcare, social programs, and post-secondary education; division of resources at provinces' discretion

1996 Royal Commission on Aboriginal Peoples
- established in the wake of the Oka Crisis. The Commission's Report, the product of extensive research and community consultation, was a broad survey of historical and contemporary relations between Aboriginal and non-Aboriginal peoples in Canada
- recommendations made on how to repair the relationship between Indigenous peoples and Canada

2001 *Kirby and Romanow Commissions* appointed
- *Kirby Commission* (final report, October 2002)
- examines history of the healthcare system in Canada, pressures and constraints of current healthcare system, role of federal government, and healthcare systems in foreign jurisdictions

Romanow Commission (final report, November 2002)
- dialogue with Canadians on the future of Canada's public healthcare system

2004 *First Ministers' Meeting on the Future of Health Care* produces a 10 year plan
- priorities include reductions in waiting times, development of a national pharmacare plan, and primary care reform

2005 *Chaoulli v. Québec*, Supreme Court of Canada decision
- rules that Québec's banning of private insurance is unconstitutional under the Québec Charter of Rights since patients cannot access the relevant services under the public system in a timely manner

2007 *Jordan's Principle*
- Jordan Anderson was a First Nations child from Norway House Cree Nation born with complex medical needs
- he spent two unnecessary years in hospital because provincial and federal governments could not decide who was responsible for paying for the home-based care that Jordan needed to be discharged. Consequently, he died in hospital at age 5 without ever going home
- *Jordan's Principle* is a legal obligation that promises that First Nations children will get prompt and equitable access to healthcare and that payments (federal/provincial/local) will be determined later
- in 2016, the Canadian Human Rights Tribunal found that the Canadian government was racially discriminating against First Nations children and their families for its failure to properly implement Jordan's Principle. The Tribunal issued legally binding orders that Canada has an obligation to fulfill

2011 First progress report by the Health Council reviews progress toward 2004 First Ministers' 10 year plan
- significant reductions in wait times for specific healthcare areas (such as cancer care, joint replacements, and sight restoration), but may have inadvertently caused increased wait times for other services
- despite large investments into EMRs, Canada continues to have low uptake, ranking last in the Commonwealth Fund International Health Policy survey, with only 37% use among primary care physicians
- minimal progress in creating a national strategy for equitable access to pharmaceuticals; however, there has been some success in increasing pharmacists' scope of practice, reducing generic drug costs, and implementing drug information systems

- increases funding to provinces at 6% per annum until the 2016-2017 fiscal year; from then onwards, increases tied to nominal GDP at a minimum of 3% per annum

2012 Second progress report by the Health Council reviews progress towards 2004 First Ministers' 10 year plan
- funding is sufficient; however, more innovation is needed including incentivizing through models of remuneration
- 46 recommendations are made to address the lack of progress

2014 Expiry of 10 Year Health Care Funding Agreement between federal and provincial governments
- *Canadian Doctors for Refugee Care v. Canada*, the Federal Court of Canada rules that the federal government could not significantly reduce/eliminate healthcare services for refugee claimants, as to do so would constitute "cruel and unusual treatment" contrary to the Charter of Rights and Freedoms

2015 Negotiations underway for a new Health Accord with a $3 billion investment over four years to homecare and mental health services by the elected Liberal government

2015 The Truth and Reconciliation Commission releases 94 "calls to action" (or recommendations) to further reconciliation between Canada and Indigenous peoples
- the full list of calls to action can be found here: https://www2.gov.bc.ca/assets/gov/british-columbians-our-governments/indigenous-people/aboriginal-peoples-documents/calls_to_action_english2.pdf, while health-specific calls and subsequent government actions can be found here: https://www.rcaanc-cirnac.gc.ca/eng/1524499024614/1557512659251
- the seven calls to action included under health are the following:
  - we call upon the federal, provincial, territorial, and Aboriginal governments to acknowledge that the current state of Aboriginal health in Canada is a direct result of previous Canadian government policies, including residential schools, and to recognize and implement the health-care rights of Aboriginal people as identified in international law, constitutional law, and under the Treaties
  - we call upon the federal government, in consultation with Aboriginal peoples, to establish measurable goals to identify and close the gaps in health outcomes between Aboriginal and non-Aboriginal communities, and to publish annual progress reports and assess longterm trends. Such efforts would focus on indicators such as: infant mortality, maternal health, suicide, mental health, addictions, life expectancy, birth rates, infant and child health issues, chronic diseases, illness and injury incidence, and the availability of appropriate health services
  - in order to address the jurisdictional disputes concerning Aboriginal people who do not reside on reserves, we call upon the federal government to recognize, respect, and address the distinct health needs of the Métis, Inuit, and off-reserve Aboriginal peoples
  - we call upon the federal government to provide sustainable funding for existing and new Aboriginal healing centres to address the physical, mental, emotional, and spiritual harms caused by residential schools, and to ensure that the funding of healing centres in Nunavut and the Northwest Territories is a priority
  - we call upon those who can effect change within the Canadian health-care system to recognize the value of Aboriginal healing practices and use them in the treatment of Aboriginal patients in collaboration with Aboriginal healers and Elders where requested by Aboriginal patients
  - we call upon all levels of government to: i. Increase the number of Aboriginal professionals working in the health-care field. ii. Ensure the retention of Aboriginal health-care providers in Aboriginal communities. iii. Provide cultural competency training for all healthcare professionals
  - we call upon medical and nursing schools in Canada to require all students to take a course dealing with Aboriginal health issues, including the history and legacy of residential schools, the United Nations Declaration on the Rights of Indigenous Peoples, Treaties and Aboriginal rights, and Indigenous teachings and practices. This will require skills-based training in intercultural competency, conflict resolution, human rights, and anti-racism

2016 Canada's Minister of Indigenous Affairs announces their full support for the *United Nations Declaration on the Rights of Indigenous Peoples*
- document describes individual and collective rights of Indigenous peoples and provides guidance about how to maintain a relationship with Indigenous peoples based on equality, partnership, good faith, and mutual respect

2017 New 10 year Canada Health Accord is reached with a $11.5 billion federal investment over 10 years to homecare and mental health services and a 3% annual rise in the Canada Health Transfer (from 6% in the previous agreement)

2019 Missing and Murdered Indigenous Women and Girls Inquiry Final Report and Calls for Justice

- reveals that persistent and deliberate human and Indigenous rights violations and abuses amount to genocide and are the root cause behind Canada's staggering rates of violence against Indigenous women, girls, and 2SLGBTQQIA+ people
- the report calls for transformative legal and social changes to resolve the crisis that has devastated Indigenous communities across the country

2019 The federal government announces the creation of a national drug agency. It will negotiate prices on behalf of Canada's drug plans, assess the efficacy of prescription drugs, and develop a nationalformulary

- this commitment is later confirmed in the 2022 Federal Budget

Healthcare Expenditure and Delivery in Canada

- the projected total healthcare expenditure in 2022 was expected to reach $331 billion, or $8563 per person. Health spending was expected to comprise 12.2% of Canada's GDP that year

Sources of Healthcare Funding

- public sector covers services offered on either a fee for service, capitation, or Alternate Payment Plan (APP) in physicians' offices and in hospitals
  - fee-for-service is a payment model where services are unbundled and paid for separately. This can serve as an incentive for physicians to provide more services because payment is dependent on the quantity of services provided
  - in Ontario, each service has a corresponding billing code defined by the Ministry of Health in the Physician Services Agreement under the *Health Insurance Act*
  - capitation is a physician remuneration payment model determined by the number of patients rostered that is used in Primary Care models
  - APP is a mutual agreement between a physician (or group of physicians) and their provincial health authority. The agreement outlines the physician's salary, incentives, and various after-hour bonuses
- public sector does not cover services provided by privately practicing health professionals (e.g. dentists, chiropractors, optometrists, massage therapists, osteopaths, physiotherapists, podiatrists, psychologists, private duty nurses, and naturopaths), prescription drugs, OTC drugs, personal health supplies, and use of residential care facilities

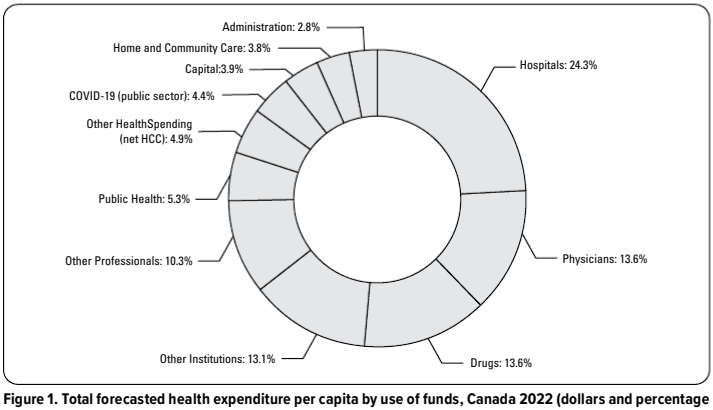

Figure 1. Total forecasted health expenditure per capita by use of funds, Canada 2022 (dollars and percentage share)

Share of total health expenditures by spending category, where Hsopitals, Physicians, and Drugs account for the largest shares of health spending

Source: National Health Expenditure Database, Canadian Institute for Health Information. Reprinted with permission of CIHI

Delivery of Healthcare

- hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities
- other countries have different systems of healthcare delivery, for example:
  - the United States has a mix of public and private funding, as well as private for-profit and private not-for-profit delivery
  - the United Kingdom has primarily public funding and delivery

Physician Licensure and Certification

Table 2. Key Physician Certification and Licensing Bodies in Canada (and Ontario)

Certifying Body	Description
MCC	Certifies physicians with the LMCC. LMCC acquired by passing the MCC Qualifying Examination Parts I and II
RCPSC	Certifies residents who complete an accredited residency program and pass the appropriate exam
	Voluntary membership of the RCPSC is designated FRCPC or FRCSC
CFPC	Certifies residents who complete an accredited family medicine residency program and pass the Certification Examination in Family Medicine
Licensing Body	13 provincial medical regulatory (licensing) authorities
	All postgraduate residents and all practicing physicians must hold an educational or practice license from the licensing body in the province in which they study or practice
CPSO	Membership to the provincial licensing authority is mandatory
	Licensing authority functions include:
	Provide non-transferable licensure to physicians
	Maintaining ethical, legal, and competency standards and developing policies to guide physicians
	Investigating complaints against physicians
	Disciplining physicians guilty of professional misconduct or incompetence
Certifying Body	At times of license investiture and renewal, physicians must disclose if they have a condition (such as substance use disorders, or other illnesses) that may impact their ability to practice safely

- physician certification is governed nationally, while the medical profession in Canada self-regulates under the authority of provincial legislation
- self-regulation is based on the premise that due to the advanced education and training involved in the practice of medicine, the lay person is not in a position to accurately judge the standards of the profession; the self-regulating colleges have a mandate to regulate the profession in the public interest
- the RCPSC and CFPC are responsible for monitoring ongoing CME and professional development
- certification by the LMCC plus either the RCPSC or CFPC is a minimum requirement for licensure by most provincial licensing authorities

Role of Professional Associations

Table 3. Key Professional Associations

Association	Description
CMA	Provides leadership to physicians and advocates for access to high quality care in Canada
	Represents physician and population concerns at the national level
	Membership is voluntary
PTMAs (such as the OMA)	Negotiates fee and benefit schedules with provincial governments
	Represents the economic and professional interests of physicians
	Membership is voluntary
	Provide physician health support
CMPA	Physician-run organization that protects the integrity of member physicians
	Provides legal defense against allegations of malpractice or negligence
	Provides risk management and educational programs
	Membership is voluntary but all physicians must have some form of liability insurance
RDoC and PHO	Upholds economic and professional interests of residents across Canada
	Facilitates discussion amongst PHOs regarding policy and advocacy items
CFMS and FMÉQ	Medical students are represented at their universities by student bodies, which collectively form the CFMS or FMÉQ
	FMÉQ membership includes that of francophone medical schools

Advocacy and Diversity

Similar to how the FMÉQ represents the interests of francophone medical schools and the CFMS represents those nation-wide, other professional associations serve and advocate on behalf of different communities

These associations may serve traditionally underrepresented groups, underserved communities, communities facing structural barriers, and/or communities with unique health needs

Some examples of professional associations that physicians or medical students may join are: Gay, Lesbian, Bisexual and Transgender (GLBT) Medical Students of Canada; the Black Medical Students Association of Canada; Black Physicians Association of Ontario (BPAO); Muslim Medical Association of Canada and the Indigenous Physicians Association of Canada (IPAC); Indigenous Medical/Dental Students Association (IMDSA, Alberta)

Ethical and Legal Issues in Canadian Medicine

Introduction to the Principles of Ethics

- ethics involve thinking about what the best course of action may be in a specific case, including:
  1. principles and values that help us consider what might be morally permissible and/or impermissible in specific circumstances
  2. rights, duties, and obligations of individuals and groups
- as a self-regulated profession, ethical and professional practice is guided by a shared code of conduct (the CMA code of ethics), and by our provincial licensing bodies (through policies)
- the physician-patient relationship significantly depends on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
- a fiduciary duty is a legal duty to act in another party's interest. Profit from the fiduciary relationship must be strictly accounted for with any improper profit (monetary or otherwise) resulting in sanctions against the physician and potential compensation to the patient, even if no physical harm has befallen the patient

Autonomy vs. Competence vs. Capacity
Autonomy: the right that patients have to make decisions according to their values, beliefs, and preferences
Competence: the ability to make a specific decision for oneself as determined legally by the courts
Capacity: the ability to make a specific decision for oneself as determined by the clinicians proposing the specific treatment

Table 4. The Four Principles Approach to Medical Ethics

Principle	Definition
Autonomy	Recognizes an individual's right to make their own decisions in their own way(s) based on their wishes, beliefs, values, and preferences
	It may not be possible for a person to make a fully autonomous decision and/or to have an autonomous decision honoured in some circumstances. For instance, if an autonomous request for a medical intervention is deemed clinically inappropriate from the physician's perspective, then the physician need not offer it
	Autonomy is not synonymous with capacity
Beneficence	Obligation to provide benefit to the patient, based on what is considered to be their best interests. Consideration of best interests should consider the patient's values, beliefs, and preferences, so far as these are known. Best interests extend beyond solely medical considerations
	May be limited by the principle of Autonomy (such as when differences exist between patient and clinician's conception of best interests)
	Paramount in situations where consent/choice is not possible
Non-Maleficence	Obligation to avoid causing harm; primum non nocere ("First, do no harm")
	A limiting principle of the Beneficence principle
Justice	Fair distribution of benefits and harms within a community, regardless of geography, income, or other social factors
	Concept of fairness: Is the patient receiving what they deserve – their fair share? Are they treated the same as equally situated patients? (equity) How does one set of treatment decisions impact others? (equality)
	Equality and equity are different notions of justice. Equality involves providing the distribution of resources to all people irrespective of differing needs, and equity involves distributing resources in a way that considers differing needs (such as circumstance and social context). Both concepts raise different considerations
	Basic human rights, such as freedom from persecution and the right to have one's interests considered and respected

Note: The four principles approach (i.e. principlism) is just one approach to medical ethics. There exist many other ethical principles that are also relevant to medicine (e.g. transparency, trust, etc.)

CMA Code of Ethics and Professionalism

- the CMA developed a Code of Ethics and Professionalism that provides standards of ethical practice to guide Canadian physicians, which covers virtues that should be exemplified by an ethical physician, fundamental commitments of the medical profession, professional responsibilities, and the relation of the physician to themselves, colleagues, and society
- the Code of Ethics and Professionalism is:
  - prepared by physicians for physicians and applies to physicians, residents, and medical students
  - informs ethical decision-making, especially where existing guidelines are insufficient or values and principles come into tension
  - not exhaustive; it is intended to provide standards of ethical practice that can be interpreted and applied in particular situations
  - founded on other principles including the Hippocratic Oath, developments in human rights, and recent bioethical discussions
- CMA policy statements address specific ethical issues/topics not mentioned by the code (e.g. abortion, transplantation, and medical assistance in dying)

The CMA Code of Ethics and Professionalism is a quasi-legal standard for physicians; if the law sets a minimal moral standard for physicians, the Code seeks to augments these standards

Table 5. CMA Code of Ethics and Professionalism

A. Virtues exemplified by the ethical physician	
Compassion Honesty Humility	Integrity Prudence
B. Fundamental commitments of the medical profession	
Commitment to the well-being of the patient Commitment to respect for persons Commitment to justice Commitment to professional integrity and competence	Commitment to professional excellence Commitment to self-care and peer support Commitment to inquiry and reflection
C. Professional responsibilities	
Physicians and patients	Patient-physician relationship Decision-making
Physicians and the practice of medicine	Patient privacy and the duty of confidentiality Managing and minimizing conflicts of interest
Physicians and self	Awareness of wellness services and promote health among self Seek support for professional and personal problems Cultivate safe training and working environments
Physicians and colleagues	Treating colleagues with respect and dignity Take responsibility for actions towards colleagues
Physicians and society	Commitment to high quality healthcare services Recognition of the social determinants of health Supporting equitable access to healthcare resources, and building collaborative relationships with marginalized groups

Confidentiality

Overview of Confidentiality

- start from the foundational assumption that all information given by the patient is both confidential (meaning it cannot be disclosed to others) and privileged (meaning it cannot be used in court), then determine whether exceptions to this exist
- the legal and ethical basis for maintaining confidentiality is that personal health information and private details of a patient's life are often required for accurate diagnosis and care of patients. As part of maintaining a therapeutic relationship, patients must trust their physician to keep this information confidential (see *Privacy of Medical Records, ELOM11*)
- privacy is a right of patients (which they may forgo), while confidentiality is a duty of physicians (which they must respect barring patient consent or requirements of the law)
- if confidentiality is inappropriately breached by a physician, that physician can be sanctioned by the hospital, court, or regulatory authority
- based on the ethical principle of autonomy, patients have the right to control their own health information and they may choose what aspects they want to disclose to their physicians
- confidentiality may be ethically and legally breached in certain circumstances (see below)
- while physician-patient privilege exists, it is limited in comparison to solicitor-client privilege. During conversations with patients about confidentiality, physicians should avoid promising absolute confidentiality or privilege, as it cannot be guaranteed by law
- legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting court cases in the common law

Legal Aspects of Confidentiality
Advice should always be sought from provincial licensing authorities, provincial/territorial privacy commissioner's offices, and/or legal counsel when in doubt

CMA Code of Ethics and Professionalism
"Fulfill your duty of confidentiality to the patient by keeping identifiable patient information confidential; collecting, using, and disclosing only as much health information as necessary to benefit the patient; and sharing information only to benefit the patient and within the patient's circle of care. Exceptions include situations where the informed consent of the patient has been obtained for disclosure or as provided for by law"

Statutory Reporting Obligations

- legislation has defined specific instances where public interest overrides the patient's right to confidentiality; varies by province, but may include:
  1. suspected child abuse or neglect – report to local child welfare authorities (e.g. Children's Aid Society)
  2. fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see Geriatric Medicine, GM14)
  3. communicable diseases – report to local public health authority (see Public Health and Preventive Medicine, PH31)
  4. improper conduct of other physicians or health professionals – report to College or regulatory body of the health professional (sexual impropriety by physicians is required reporting in some provinces)
  5. vital statistics must be reported; reporting varies by province (e.g. in Ontario, births are required to be reported within 30 d to the Office of Registrar General or local municipality; death certificates must be completed by a physician then forwarded to municipal authorities)
  6. reporting to coroners (see *Physician Responsibilities Regarding Death, ELOM21*)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

Duty to Protect/Warn

- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detainment of patients for clinical assessment), informing the police, and/or warning the potential victim(s) if a patient expresses an intent to harm
- Canadian courts have not expressly imposed a mandatory duty to report, however, the CMA Code of Ethics and some provincial/territorial regulatory authorities may oblige physicians to report (mandatory reporting rather than permissive)
- concerns of breaching confidentiality should not prevent the physician from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
- applies in a situation where:
    1. there is an imminent risk
    2. to an identifiable person or group
    3. of serious bodily harm or death

Ontario's Medical Expert Panel on Duty to Warn
CMAJ 1998;158(11):1473-1479
There should be a duty to inform when a patient reveals that they intend to do serious harm to another person(s) and it is more likely than not that the threat will be carried out

Where a threat is directed at a person or group and there is a specific plan that is concrete and capable of commission and the method for carrying it out is available to the threatener, the physician should immediately notify the police and, in appropriate circumstances, the potential victim. The report should include the threat, the situation, the physician's opinion, and the information upon which it is based

While Canadian courts have not expressly imposed a mandatory "duty to warn" on physicians to alert third parties of a danger posed by a patient, Canadian supreme court decisions have held that a physician is permitted to warn (permissive vs. mandatory)

Disclosure for Legal Proceedings

- disclosure of health records can be compelled by a court order, warrant, or subpoena

Privacy of Medical Records

- privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the Canadian Charter of Rights and Freedoms, and the physician's fiduciary duty
- the federal government created the PIPEDA in 2000 which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, and private labs)
- PIPEDA has been superseded by provincial legislation in many provinces, such as the Ontario *Personal Health Information Protection Act*, which applies more specifically to health information

Duties of Physicians with Regard to the Privacy of Health Information

- inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
- obtain the patient's expressed consent to disclose information to third parties
    - under Ontario privacy legislation, the patient's expressed consent need not be obtained to share information between healthcare team members involved in the "circle of care." However, the patient may withdraw consent for this sharing of information and may put parts of the chart in a "lock box"
    - physicians have a professional obligation to facilitate timely transmission of the patient's medical record to third parties (with the patient's consent), such as for insurance claims. Failure to do so has resulted in sanctions by regulatory bodies
    - while patients have a right of access to their medical records, physicians can charge a "reasonable fee" commensurate with the time and material used in providing copies/access
- provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
- provide secure storage of information and implement measures to limit access to patient records
- ensure proper destruction of information that is no longer necessary
- regarding taking pictures or videos of patients, findings, or procedures, in addition to patient consent and privacy laws, trespassing laws apply in some provinces
- in addition to Ontario legislation and case law, the CPSO policy sets out professional expectations of physicians regarding the handling of personal health information. This includes regulations regarding express or implied consent, incapacity, lock boxes, disclosure under exceptional circumstances, mandatory reporting, ministry audits, subpoenas, court orders, and police, as well as electronic records and voice messaging communication: https://www.cpso.on.ca/Physicians/Policies-Guidance/Policies/Protecting-Personal-Health-Information
- it is the physician's responsibility to ensure appropriate security provisions with respect to electronic records and communications
    - with the advent of digital records, there have been increasing issues with healthcare providers that are not part of a patient's circle of care accessing medical records inappropriately (e.g. out of curiosity or for profit). All staff and learners should be aware that most EMRs log which healthcare providers view records and automatically flag files for further review in certain cases (e.g. same surname, VIP patients, or audit of access to records). Regular audits are completed specifically to look for unauthorised access to records. This includes accessing personal health information of friends and family.

CMA Code of Ethics and Professionalism
Protect the health information of your patients

Provide information reasonable in the circumstances to patients about the reasons for the collection, use, and disclosure of their health information

Be aware of your patients' rights with respect to the collection, use, disclosure, and access to their health information; ensure that such information is recorded accurately

Lock Boxes
The term "lock boxes" applies to situations where the patient has expressly restricted their physician from disclosing specific aspects of their health information to others, even those involved in the patient's circle of care. Note that the Personal Health Information Protection Act (PHIPA) provisions denote that patients may not prevent physicians from disclosing personal health information permitted/required by the law

Consequences of a Breach of Privacy

- PHIPA outlines which privacy breaches must be reported to the Information and Privacy Commissioner of Ontario
- to underscore the importance of maintaining confidentiality and privacy the fines for breaches was increased in 2020
- an individual who commits a breach may be fined up to $200000 or a year in prison or both. An institution can be fined up to $1000000
- beyond financial implications, breaches in confidentiality and privacy erode the trust of the patient involved and greater society's trust of the profession

Reasons to Breach Confidentiality
Child abuse
Fitness to drive
Communicable disease
Coroner report
Duty to inform/warn

Consent and Capacity

Ethical Principles Underlying Consent and Capacity from the Ontario Health Care Consent Act

- consent is the autonomous authorization of a medical intervention by a patient or their substitute decision-maker
- informed consent is a process, not a transaction or a signature on a page
- informed refusal is equivalent in principle and approach
- if a patient is deemed incapable of consenting to a proposed medical intervention, then it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
- there is a duty to discover, if possible, what the patient would have wanted when capable
- central to determining best interests is understanding and taking into account the patient's values, beliefs, and preferences, including any relevant cultural and/or religious considerations and the patient's interpretation of those considerations
- more recently expressed wishes take priority over remote ones
- patient wishes may be expressed verbally or in written form
- patients found incapable of making a specific decision should still be involved in the decision-making process as much as possible. If a patient found incapable expresses a willingness to pursue the proposed treatment/intervention, then this is known as assent (rather than 'consent,' which requires capacity)
- agreement or disagreement with medical advice does not determine findings of capacity/incapacity
- however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed. Steer clear from the tendency to define what reasonable person standards may be. If appropriate, look to discern patterns of justification offered by patients and their individual values and beliefs, which may be influenced by social context, such as culture and/or religion
- laws pertaining to consent and capacity may vary by province/territory and readers are encouraged to consult provincial/territorial guidelines

Four Basic Requirements of Valid Consent

1. Voluntary
- consent must be given free of coercion or pressure (e.g. from family members who might exert 'undue influence,' from members of the clinical team)
- the physician must not deliberately mislead the patient about the proposed treatment
- the physician must engage in self-reflection prior to entering the conversation regarding their position of power and privilege as well as take measures to mitigate the power differential within the relationship
- consent is continuous and a patient may change their mind at any point

2. Capable
- the patient must be able to understand and appreciate the nature and effect of their condition as well as of the proposed treatment or decision

3. Specific
- the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (e.g. the patient must be informed if students will be involved in providing the treatment)

4. Informed
- sufficient information and time must be provided to allow the patient to make choices in accordance with their wishes, including:
  - the nature of the treatment or investigation proposed and its expected effects
  - all significant risks and special or unusual risks
  - disclose common adverse events and all serious risks (e.g. death), even if remote
  - alternative treatments or investigations and their anticipated effects and significant risks
  - the consequences of declining treatment
  - answers to any questions the patient may have
- the reasonable person test – the physician must provide all information that would be needed "by a reasonable person in the patient's position" to be able to make a decision
- it is the physician's responsibility to make reasonable attempts to ensure that the patient understands the information, including overcoming language barriers, or communication challenges
- physicians have a duty to inform the patient of all legitimate therapeutic options and must not withhold information based on conscientious objections (e.g. not discussing the option of emergency contraception)

Health Care Consent Act
Obtaining valid consent before carrying out medical, therapeutic, and diagnostic procedures has long been recognized as an elementary step in fulfilling the physician's obligations to the patient Capacity is an essential component of valid consent, and obtaining valid consent is a policy of the CMA and other professional bodies

4 Basic Elements of Consent
Voluntary
Capable
Specific
Informed

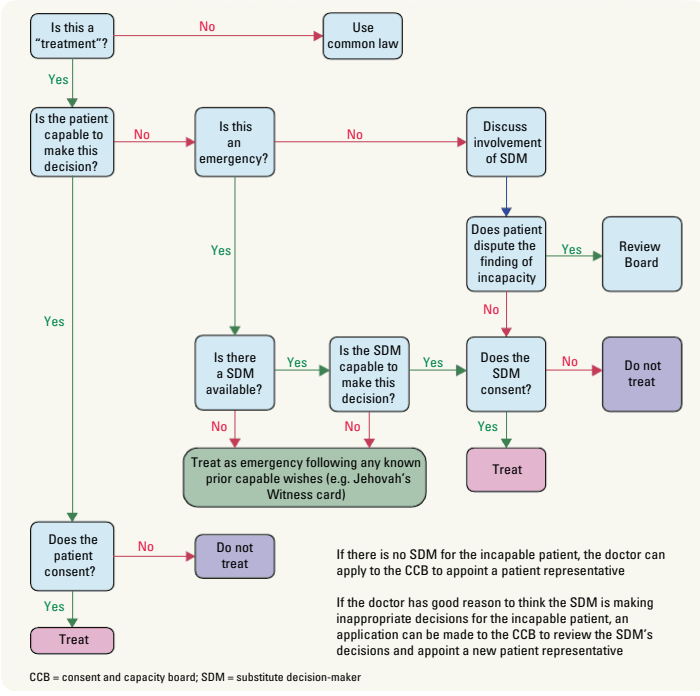
Is this a "treatment"?
No
Use common law
Yes
Is the patient capable to make this decision?
No
Is this an emergency?
No
Discuss involvement of SDM
Does patient dispute the finding of incapacity
Yes
Review Board
No
Yes
Yes
Is there a SDM available?
Yes
Is the SDM capable to make this decision?
Yes
Does the SDM consent?
No
Do not treat
No
No
Yes
Treat as emergency following any known prior capable wishes (e.g. Jehovah's Witness card)
Treat
Does the patient consent?
No
Do not treat
Yes
Treat
If there is no SDM for the incapable patient, the doctor can apply to the CCB to appoint a patient representative
If the doctor has good reason to think the SDM is making inappropriate decisions for the incapable patient, an application can be made to the CCB to review the SDM's decisions and appoint a new patient representative
CCB = consent and capacity board; SDM = substitute decision-maker

Figure 2. Ontario consent flowchart
Adapted by Hébert P from Sunnybrook Health Sciences Centre Consent Guidelines

Obtaining Legal Consent

- consent of the patient must be obtained before any medical intervention is provided; consent can be:
  - verbal or written, although written is usually preferred
  - a signed consent form is only evidence of consent – it does not replace the process for obtaining valid consent
  - most important component is what the patient understands and appreciates, not what the signed consent form states
  - implied (e.g. a patient holding out their arm for an immunization) or expressed
  - consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm, and the patient is not informed of and/or capable of considering these harms
  - if consent has been withdrawn during a procedure, the physician must stop treatment unless stopping the procedure would threaten the patient's life
  - in obtaining consent to continue the procedure, the physician need only re-explain the procedure and risks if there has been a material change in circumstances since obtaining consent originally. If there has been no material change in circumstances, simple assent to continue is sufficient (*Ciarlariello v. Schachter*)
- HCCA of Ontario (1996) covers consent to treatment, admission to a facility, and personal assistance services (e.g. home care)

Exceptions to Consent

1. Emergencies

- treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their SDM
- emergency treatment should not violate a prior expressed wish of the patient (e.g. a signed Jehovah's Witness card)
- if patient is incapable, the physician must document reasons for incapacity and why the situation is emergent
- patients have a right to challenge a finding of incapacity as it removes their decision-making ability
- if a SDM is not available, the physician can treat without consent until the SDM is available or the situation is no longer emergent

2. Legislation
- mental health legislation allows for:
  - the detention of patients without their consent
  - psychiatric outpatients may be required to adhere to a care plan in accordance with community treatment orders
- Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases

3. Special Situations
- public health emergencies (e.g. an epidemic or communicable disease treatment)
- warrant for information by police

Consequences of Failure to Obtain Valid Consent
- treatment without consent is battery (a claim in tort, meaning a civil legal matter, as opposed to a criminal legal matter), even if the treatment is life-saving (excluding situations outlined in Exceptions to Consent)
- treatment of a patient on the basis of poorly informed consent may constitute negligence, also a claim in tort
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)

Overview of Capacity
- capacity is the ability to:
  - understand information relevant to a treatment decision
  - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
- capacity is specific for each decision (e.g. a person may be capable to consent to having a CXR, but not for a bronchoscopy)
- capacity can change over time (e.g. temporary incapacity secondary to delirium)
- most Canadian jurisdictions distinguish capacity to make healthcare decisions from capacity to make financial decisions; a patient may be deemed capable of one, but not the other
- a person is presumed capable unless there is good evidence to the contrary
- capable patients are entitled to make their own decisions
- capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny

Assessment of Capacity
- the person undergoing the assessment of capacity must be informed that they will be assessed
- capacity assessments must be conducted by the clinician providing treatment and, if appropriate, in consultation with other healthcare professionals (e.g. another physician or interprofessional healthcare provider)
- clinical capacity assessment may include specific capacity assessment (i.e. capacity specific to the decision at hand):
  1. effective disclosure of information and evaluation of patient's reason for decision
  2. understanding of:
     - the condition
     - the nature of the proposed treatment
     - alternatives to the treatment
     - the consequences of accepting and rejecting the treatment
     - the risks and benefits of the various options
  3. for the appreciation needed for decision-making capacity, a person must:
     - acknowledge the symptoms that affect them
     - be able to assess how the various options would affect them
     - be able to reach a decision, and make a choice, not based primarily upon delusional belief
- general impressions
- input from psychiatrists, neurologists, etc. for any underlying mental health or neurological condition that may affect insight or decision-making
- employ "Aid to Capacity Evaluation" or any other capacity assessment tool/guideline
- a decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board (CCB)), or the courts; the patient has the right to a hearing before the CCB
- if found incapable by the Consent and Capacity Review Board, patient must receive notice of their ability to pursue judicial review (and essentially appeal the determination)

Treatment of the Incapable Patient in a Non-Emergent Situation
- obtain informed consent from SDM
- important to distinguish the cause of incapacity (mental illness vs other) to determine appropriate legislation. The Mental Health Act only covers detention and treatment of patients with specific conditions
- an incapable patient can only be detained against their will to receive treatment if they meet criteria for certification under the Mental Health Act (see Psychiatry, PS61); in such a situation:
  - document assessment in chart
  - notify patient of assessment using appropriate Mental Health form(s) under the Mental Health Act (Form 42 or Form 30 in Ontario)
  - notify Rights Advisor

Aid to Capacity Evaluation
J Gen Intern Med 1999;14(1):27-34

Ability to understand the medical problem

Ability to understand the proposed treatment

Ability to understand the alternatives (if any) to the proposed treatment

Ability to understand the option of refusing treatment or of it being withheld or withdrawn

Ability to appreciate the reasonably foreseeable consequences of accepting the proposed treatment

Ability to appreciate the reasonably foreseeable consequences of refusing the proposed treatment

Ability to make a decision that is not substantially based on delusions or depression

Capacity Assessment Criteria in Ontario
Test for understanding: can the patient explain the information you have given them in their own words?
Test for appreciation: can they explain how that information relates to them personally?
Refer to: JAMA The Rational Clinical Examination "Does This Patient Have Medical Decision-Making Capacity?

Incapable Patient
Note: Capacity is treatment-specific and time-specific. An incapable patient is only incapable for the specific treatment at the specific time
If not already present, perform a formal capacity assessment and thoroughly document
Identify if the patient has an SDM or who has their POA and locate it, if applicable
Check the patient's chart for any Mental Health Forms (e.g. Form 1) or any forms they may have on their person (e.g. Form 42)

Pediatric and Adolescent Patients

- no age of consent in all provinces and territories except Québec; Québec has a specific age of consent, but common law and case law deem underage legal minors capable, allowing these individuals to make their own choices
- consent depends on patient's decision-making capacity and must pass the same understand and appreciate test
- infants and young children are assumed to lack mature decision-making capacity for consent but they should still be involved in decision-making processes when appropriate (i.e. be provided with information appropriate to their comprehension level)
- preferably, assent should still be obtained from patient, even if not capable of giving consent
- in the event that the physician believes the SDM is not acting in the child's best interests, an appeal must be made to the local child welfare authorities
- under most circumstances, parents have the right of access to the child's medical record. If the child is able to consent to a treatment, they are also the one to determine who has access to their medical records related to that treatment

There is no age of consent in Ontario
Capacity is determined the ability to understand and appreciate test

Substitute Decision-Makers

- Substitute decision-makers (SDMs) is the person (or persons) who is legally permitted to make healthcare decisions on behalf of an incapable person
- The person who may fulfil this role is outlined in the Health Care Consent Act (HCCA) in Ontario (please check relevant legislation for other provinces)
- In Ontario, the automatic SDM is the closest living relative by blood, marriage or adoption. SDM's can be appointed through a legal process that supercede these automatic ones (Court Appointed Guardian, Attorney for Personal Care and Representative appointed by the Consent and Capacity Board) A full list of the hierarchy can be found in the HCCA
- SDMs must adhere to the following principles when giving informed consent on behalf of an incapable patient:
  - act in accordance with any wishes that the person expressed when capable
  - if wishes unknown, act in the patient's best interest, taking the following into account:
    1. values and beliefs held by the patient while capable
    2. whether well-being is likely to improve with vs. without treatment
    3. whether the expected benefit(s) outweighs the risk of harm
    4. whether a less intrusive treatment would be as beneficial as the one proposed
- the final decision of the SDM may and should be challenged by the physician if the physician believes the SDM is not abiding by the above principles

Most provinces have legislated hierarchies for SDMs; the hierarchy in Ontario is:

Legally appointed guardian

Appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see *Powers of Attorney*)

Representative appointed by the Consent and Capacity Board

Spouse or common law partner

Child (age 16 or older) and parent (unless the parent has only a right of access)

Parent with only a right of access

Sibling

Other relative(s)

Public guardian and trustee

POWERS OF ATTORNEY

- all Guardians and Attorneys have fiduciary duties for the dependent person

Definitions

- **Power of Attorney for Personal Care**
  - a legal document in which one person gives another the authority to make personal care decisions (healthcare, nutrition, shelter, clothing, hygiene, and safety) on their behalf if they become a person with mental incapacity. An Attorney for Personal Care is a substitute decision-maker and they are the third highest on the SDM hierarchy above automatic SDMs
- **Guardian of the Person**
  - someone who is appointed by the court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care. The Guardian is a substitute decision-maker and they are the highest on the SDM hierarchy above automatic SDMs
- **Continuing Power of Attorney for Property**
  - legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions.
- **Guardian of Property**
  - someone who is appointed by the Public Guardian and Trustee or the courts to look after an incapable person's property or finances
- **Public Guardian and Trustee**
  - acts as a SDM of last resort on behalf of a person with a mental incapacity who do not have another individual to act on their behalf

Other Types of Capacity Not Covered by the HCCA

Testamentary (ability to make a will)

Fitness (ability to stand trial)

Financial (ability to manage property – Form 21 of the Mental Health Act)

Personal (ability to care for oneself on a daily basis)

Substitute consent for a procedure whose primary purpose is research, sterilization for non-therapeutic purposes, or removal of organs or tissue for transplantation (does not apply to those already declared dead)

Negligence

Ethical Basis

- the physician-patient relationship is primarily based on trust, which is recognized in the concept of fiduciary duty, the responsibility to act in the patient's best interest
- negligence or malpractice is a form of failure on the part of the physician in fulfilling their fiduciary duty in providing appropriate care and leading to harm of the patient (and/or abuse of patient's trust)

Legal Basis

- physicians are legally liable to their patients for causing harm (tort) through a failure to meet the standard of care applicable under the circumstances

- standard/duty of care is defined as one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, specialization, and standing
- liability arises from physicians' common law duty of care to their patients in the physician/patient relationship (or in Québec, from the Civil Code provisions regarding general civil liability)
- action(s) in negligence (or civil liability) against a physician must be launched by a patient within a specific prescribed period required by the respective province in which the actions occurred

Truth-Telling

Ethical Basis

- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed and autonomous decisions about healthcare and their lives

Legal Basis

- required for valid patient consent (see *Consent and Capacity, ELOM12*)
- goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision ("standard of disclosure")
- withholding information can be a breach of fiduciary duty and duty of care
- obtaining consent based on misleading information and/or insufficient information can be seen as negligent and/or coercive

Evidence about Truth-Telling

- it is a patient's right to have the option of knowing about any clinical condition(s)/diagnoses that they may have
- most patients want to be provided with information regarding their health
- although some patients may want to protect family members from bad news, they themselves would want to be informed in the same situation
- truth-telling improves trust, adherence, and health outcomes
- informed patients are more satisfied with their care and most often receive news about their health better than expected
- potential negative consequences of truth-telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability
- healthcare providers must be cautious to not apply their own personal values concerning the risk and benefits of truth telling.

CPSO Policy on Truth-Telling
Physicians should provide patients with whatever information that will, from the patient's perspective, have a bearing on medical decision-making and communicate that information in a way that is comprehensible to the patient

Medical Error

- medical error may be defined as 'preventable adverse events (AEs)' caused by the patient's medical care and not the patient's underlying illness; some errors may be identified before they harm the patient, so not all errors are truly 'adverse'
- many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient's decision-maker(s) and reported to the appropriate health authorities
- physicians must disclose to patients the occurrence of AEs or errors caused by medical management, but should not suggest that they resulted from negligence because:
  - negligence is a legal determination
  - error is not equal to negligence
- disclosure allows the injured patient to seek appropriate corrective treatment promptly if possible
- physicians should avoid simple attributions as to the cause and sole responsibility of others or oneself
- physicians should offer apologies or empathic expressions of regret (e.g. "I wish things had turned out differently") as these may help to maintain and/or rebuild trust and are not admissions of guilt or liability
- Apology Acts across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence

Errors of care are compatible with non-negligent care if they are ones that a reasonably cautious and skilled physician could make (i.e. mistakes can be made due to 'honest error')

Adverse Event
An unintended injury or complication from health care management resulting in disability, death, or prolonged hospital stay

Breaking Bad News

- 'bad news' may be any information that reveals conditions or illnesses threatening the patient's sense of well-being; different patients may classify 'bad news' in different ways
- disclosing medical information in a poor or insensitive manner may be as harmful as non-disclosure
  - caution patients in advance of serious tests and about the possibility of bad findings
  - give time for patient to reflect upon the situation prior to disclosing such news
  - give warnings of impending bad news by reviewing prior discussions
  - provide time for the patient to ask questions
  - adequate supports and strategies should always be provided following the disclosure of difficult news
- **SPIKES** protocol was developed to facilitate "breaking bad news" in a conscientious and effective manner
  - **S**etting, **P**erceptions, **I**nvitation, **K**nowledge, **E**mpathy, **S**trategy (see Palliative Medicine, PM6)
  - other tools such as the Serious Illness Conversation Guide or Vital Talk can also assist with conversations with patients with serious illness

Examples of Warning of Impending Bad News
Remember to clarify (invite) the level of knowledge desired by the patient
"I have something difficult to tell you..."
"Unfortunately, the results are not what we were hoping for..."
"This may come as a shock to you, but the tests indicate..."
"There is no easy way for me to tell you this, so I will tell you straight away that you have a serious problem..."

Arguments Against Truth-Telling
- may go against certain cultural norms and expectations
- may lead to patient harm, but only in extreme, rare situations
- medical uncertainty may result in the disclosure of uncertain or inaccurate information

Reproductive Technologies

- people of all gender identities may access reproductive technologies
- the words "maternal, mother, and woman" may refer to gender diverse individuals

Overview of Pregnancy Considerations
- medico-legally, the maternal body and the fetal body are considered one. In general, the individual who is pregnant and the fetus's interests align unless otherwise indicated via appropriate consent processes, maternal health takes precedence

Ethical Issues and Arguments
- principle of reproductive autonomy:
  - pregnant individuals have the right to reproductive choice (e.g. to make decisions that align with their personal values, interests, and beliefs)
  - coercion of an individual to accept medical advice is an unacceptable infringement of their personal autonomy. It is important to empower individuals to make informed decisions about their medical care in relation to pregnancy. This involves providing the individual with information about any relevant benefits and risks in relation to recommendations, giving them time to ask questions and reflect upon the recommendation(s), etc. A fine, but important, line exists between making a strong recommendation and coercing an individual into consenting to a medical recommendation, the latter of which must be avoided. A recommendation is, precisely, a recommendation (not forced)
  - Canada's colonial history includes a legacy of infringement of reproductive rights. It is important to be mindful of one's own inherent power and privilege when engaging in conversations
  - biases: it is important to be cognizant of one's potential biases in relation to reproductive decision-making. Ensuring that one's personal values and preferences do not unduly influence a patient's decision-making process is of the utmost importance in order to enable autonomous decision-making

Legal Issues and Arguments
- the law protects a gestating individual's right to life, liberty, and security of person. Key aspects of the gestating individual's rights include:
  - an individual with capacity (recognizing that capacity is decision- and time-specific) has the right to consent or refuse to consent to any medical recommendations irrespective of whether or not they are gestating. It is up to the treatment-proposing clinician to ensure that all relevant information related to a medical recommendation (e.g. risks, benefits) is provided to help ensure informed decision-making
  - the fetus does not have legal rights until it is born alive and with complete delivery
  - a pregnant person with comorbid substance use disorder cannot be detained and treated to protect the fetus (*Winnipeg Child and Family Services (Northwest Area) v. G. (D.F.), [1997] 3 S.C.R. 925*)
  - a fetus is not a "human being" within the meaning of the Criminal Code of Canada, thus medical negligence during delivery resulting in the death of a fetus that has not been born alive does not *constitute* criminal negligence causing death (manslaughter) and cannot attract criminal penalties (*R v Sullivan*)

Assisted Human Reproduction Act (2004) Principles
- The Parliament of Canada recognizes and declares that
  - (a) the health and well-being of children born through the application of assisted human reproductive technologies must be given priority in all decisions respecting their use;
  - (b) the benefits of assisted human reproductive technologies and related research for individuals, for families and for society in general can be most effectively secured by taking appropriate measures for the protection and promotion of human health, safety, dignity and rights in the use of these technologies and in related research;
  - (c) while all persons are affected by these technologies, women more than men are directly and significantly affected by their application and the health and well-being of women must be protected in the application of these technologies;
  - (d) the principle of free and informed consent must be promoted and applied as a fundamental condition of the use of human reproductive technologies;
  - (e) persons who seek to undergo assisted reproduction procedures must not be discriminated against, including on the basis of their sexual orientation or marital status;
  - (f) trade in the reproductive capabilities of women and men and the exploitation of children, women and men for commercial ends raise health and ethical concerns that justify their prohibition; and
  - (g) human individuality and diversity, and the integrity of the human genome, must be preserved and protected

The Tri-Council Policy Statement
1. Genetic treatment aimed at altering germ cells is prohibited in Canada and elsewhere
2. Embryo research is permitted up to 14 d post-fertilization
3. Embryos created for reproductive purposes that are no longer required may be used
4. Gamete providers must give free and informed consent for research use
5. No commercial transactions in the creation and use of the embryos are permitted
6. Creation of embryos solely for research purposes is prohibited
7. Human cloning is strictly prohibited
8. Risks of coercion must be minimized (i.e. the fertility treatment team may not be pressured to generate more embryos than necessary)
9. One may only discuss the option of using fetal tissue for research after the patient makes a free and informed choice to have a therapeutic abortion
10. Physicians responsible for fertility treatment may not be part of a stem cell research team

Assisted Reproductive Therapies
- includes non-coital insemination, hormonal ovarian stimulation, and IVF
- some commonly referenced, ethically complex topics related to assisted reproductive therapies (ART) include, but are not limited to:
  - donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical history)
  - preimplantation genetic testing for diagnosis before pregnancy
  - use of new techniques without patients appreciating their experimental nature
  - moral status of embryo
  - access to ART
  - private vs. public funding of ART
  - social justice factors influencing one's access to and/or experiences with ART (e.g. same-sex couples having an opportunity to access welcoming, morally safe 2SLGBTQQIA+ spaces to receive care)
  - the 'commercialization' of reproduction (e.g. surrogates)

Fetal Tissue
- pluripotent stem cells can currently be derived from human embryonic and fetal tissue
- use of stem cells in research is reviewed by the Stem Cell Oversight Committee as part of the CIHR
- potential uses of stem cells in research:
  - studying human development and factors that direct cell specialization
  - evaluating drugs for efficacy and safety in human models
  - cell therapy: using stem cells grown in vitro to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson's disease)
  - genetic treatment aimed at altering somatic cells (e.g. myocardial or immunological cells) is acceptable and ongoing

Induced Abortion
- CMA definition of induced abortion: the active termination of a pregnancy before fetal viability (fetus >500 g or >20 wk GA)
- full CMA policy on induced abortion can be accessed here: https://www.cmaj.ca/content/139/12/1176a
- after a CMAJ publication in 2006, several letters to the editor were published, questioning the CMA's position on induced abortion. In response, the CMA published clarification of their stance. This clarification can be accessed here: Clarification of the CMA's position concerning induced abortion | CMAJ (a)

Ethical and Legal Concerns and Arguments
- in Canada, there is no criminal prohibition regarding abortion
- termination of pregnancy is a medical and personal decision to be made in consultation with a healthcare provider, alongside anyone else the patient wishes
- there exist various reasons as to why a person may inquire about and choose to pursue termination of pregnancy
- termination of pregnancy is a value-laden and moralized topic. Healthcare providers, even those who conscientiously object to termination of pregnancy, ought to treat all patients requesting such termination with dignity, respect, and in a person-centred manner. It is of particular importance to be cognizant of one's own biases when caring for patients who want to receive a medical treatment that does not accord with one's personal belief system and preferences
- if a medical practitioner does not provide termination of pregnancy, an effective referral to a willing and available provider must be made without delay. From an ethics perspective, it is important to demonstrate continued trustworthiness and support, recognizing that trusting one's providers can influence health outcomes
- 2nd and 3rd trimester abortions are legal in Canada, but are usually, though not exclusively, pursued when there are risks to the person's health, if the fetus died in utero, and/or if the fetus has a known major irreversible condition which may subject them to poor health outcomes upon birth (e.g. anencephaly). In any of these cases, however, it is the choice of the pregnant individual as to whether or not they will maintain or terminate pregnancy

Prenatal/Antenatal Genetic Testing
- uses:
  1. to confirm a clinical diagnosis
  2. to detect genetic predisposition to a disease
  3. genetic testing/learning of predispositions may allow for preventative steps to be taken and help the person prepare for the future
  4. gives parents the option to terminate a pregnancy or begin early treatment if/as applicable
  - ethical dilemmas may arise because of the sensitive nature of genetic information; important ethical complexities and considerations related to genetic testing may include:
    - the individual and familial implications (e.g. how will learning about information confirmed via genetic testing influence one's family dynamic?)
    - its pertinence to future disease
    - its ability to identify disorders for which there are no effective treatments or preventive steps (e.g. should a person know if they/their fetus is genetically predisposed to an incurable disease? Would the potential harms of knowing this information potentially outweigh the benefits?)

- its ability to identify the sex of the fetus, which may or may not be desired and/or relevant information to one's decision-making
- obtaining truly informed consent is difficult due to the complexity of genetic information and the inability to know precisely what will/will not occur as a result of such testing (e.g. people may receive unexpected and unwanted genetic information after consenting to the testing)
- related to the above, consent to genetic testing and consent to disclosure of all genetic information that results from the test may be distinct
- some patients may want to be informed of genetic test results in particular ways (e.g. with a support person present). In the case of delivering complex information, genetic counselling may be recommended
- duty to maintain confidentiality vs. duty to warn family members (e.g. if a patient's sister is likely predisposed to the same genetic condition as your patient, what are your responsibilities to the sister, if any?)
- risk of psychological harm
- risk of experiencing unjust social discrimination if such genetic information is disclosed to certain parties

Legal Aspects

- as of 2017, the Genetic Non-Discrimination Act exists
- genetic testing requires informed consent
- physicians are obligated to inform patients that prenatal testing exists and is available
- in some specific circumstances, a physician may be able to breach confidentiality in order to warn family members about a condition if harm can possibly be prevented via treatment or prevention. In general, the patient's consent is required, unless the harm to be avoided is sufficiently serious to rise to the level of imminent risk of serious bodily harm or death (i.e. not a chronic condition, but an acute life-threatening condition). It is recommended to consult with legal counsel and bioethics if complexities arise in regard to breach of confidentiality/duty to warn

End-of-Life Care

Overview of Palliative and End-of-Life Care

- focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, and loved ones
  - palliative care is an approach that improves the quality of life of patients facing life-threatening illness, through the prevention and relief of suffering, including treating pain, physical, psychosocial, and spiritual concerns
  - *early* palliative care leads to improved quality of life and mood, fewer aggressive end-of-life treatments, and extended median survival time compared to patients receiving standard care
- appropriate for any patient at any stage of a serious or life-limiting illness
- may occur in a hospital, hospice, in the community, or at home
- often involves an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care
- palliative sedation: the use of sedative medications for patients that are terminally ill to relieve suffering and manage symptoms
- withdrawing or withholding life sustaining interventions (e.g. artificial ventilation or nutrition) that are keeping the patient alive but no longer wanted or indicated

Palliative Care – Not the Same as Medical Assistance in Dying
Palliative care is an approach designed to improve symptoms and quality of life for the duration of a person's life, but unlike Medical Assistance in Dying, it does not aim directly at or intend to end the person's life. Many palliative care physicians are incorporating MAID into their practice, though some may conscientiously object

Medical Assistance in Dying

- medical assistance in dying: the administering or prescribing for self-administration, by a medical practitioner or nurse practitioner, of a substance, at the request of a person, that causes their death

Common Ethical Arguments/Opinions

- criminally prohibiting medical assistance in dying may influence some individuals to end their own lives and/or to endure intolerable suffering until their natural death occurs
- patient has the right to make autonomous choices about the time of their own death
- belief that there is no ethical difference between the acts of euthanasia/assisted suicide and forgoing life-sustaining treatments
- belief that these acts benefit terminally ill patients by relieving suffering
- belief that patient autonomy has limits and that one cannot and/or should not be allowed to make an autonomous request to end one's life
- death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death
- an argument presented in the Carter case (see below) suggested permitting MAID will detract support for palliative care, since with proper palliative care, the number of requests for MAID would decrease. This argument was rejected in *Carter v. Canada*, as it was deemed unacceptable to make people suffer intolerably to potentially improve and/or increase support for palliative care

Legal Aspect

- in the *Carter v. Canada* decision of February 2015, the criminal prohibition on assistance in suicide was ruled unconstitutional to the extent that they prohibit physician-assisted death for a competent adult person who (1) clearly consents to the termination of life and (2) has a grievous and irremediable medical condition that causes enduring suffering that is intolerable to the individual in the circumstances of his or her condition
- Bill C-14 (June 17, 2016) legalized MAID by amending the Criminal Code to create exemptions permitting medical practitioners to provide MAID, specified the eligibility criteria, safeguards, and required documentation and authorization from the Minister of Health, as well as new offences for failure to comply with the new regulations. As the Bill C-14 criteria are narrower than the Carter decision, there are ongoing constitutional challenges to the MAID framework as it currently stands
- Bill C-39 (March 9, 2023) temporarily postpones MAID eligibility for persons suffering solely from mental illness to March 17, 2024

Bill C-14 Criteria for MAID

- patient is eligible for publicly-funded health services in Canada
- at least 18 yr, and has capacity for clear and freely given consent
- grievous and irremediable medical condition: in an advanced state of irreversible decline in capability
- suffering intolerable to the patient, not relieved under conditions they consider acceptable
- recent update eliminated criteria of "reasonable foreseeability of natural death"
- MAID process:
  1. eligibility criteria satisfied
  2. patient signs and dates a written request for MAID
  3. two independent witnesses sign the written request. Witnesses must be 18 y/o, understand the nature of MAID, and must not a) benefit (financially or otherwise) from the death, b) be an owner or operator of the healthcare facility where the patient is receiving care, c) be directly involved in the provision of health or personal care of the patient
  4. healthcare provider must inform the patient that they can withdraw their consent at any time
  5. two independent assessors (physician or nurse practitioner) must provide written confirmation that eligibility criteria are met
  6. 10 clear days must elapse between the request and the day on which MAID is provided, unless both healthcare providers agree that a shorter period is appropriate due to the patient's imminent death or loss of capacity
  7. as per the new MAID legislation (updated in 2021), a patient may request MAID even if death is not reasonably foreseeable. For a patient whose death is not reasonably foreseeable, their eligibility assessment must be a minimum of 90 days unless the assessments are completed sooner and the patient is at immediate risk of losing the capacity to consent.
  8. throughout the 10 or 90 day period and immediately before providing MAID, the healthcare provider must give the individual an opportunity to withdraw the request and ensure that the patient gives express consent to receive MAID
     - contravention of this process is an offence punishable by up to 5 yr in prison
  9. as of changes to the legislation in 2021, a patient may waive the requirement for giving final consent just before MAID is administered only if: (1) the patient's death is reasonably foreseeable and (2) while the patient has decision-making capacity the patient is:
     (a) assessed and approved for MAID
     (b) advised that they are at risk of losing capacity to provide final consent and
     (c) the patient makes a written arrangement with their health care provider where they consent in advance to receive MAID on a chosen date if they (i.e. the patient) no longer has capacity to consent on that date

Usage of Palliative and End-of-Life Care

- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from MAID as it is seen as allowing the underlying disease to take its 'natural course,' but this distinction may be more theoretical than real
- consent for withdrawal of life-support must be sought from the capable patient, or in case of incapable patient the SDMs, as per the Health Care Consent Act and Substitute Decisions Act, and as re-affirmed by the ruling in Cuthbertson v. Rasouli in 2013, as palliative care would be instituted and consent for that would require SDM consent
- refusals of care by the patient that may lead to death as well as requests for a hastened death, ought to be carefully explored by the physician to rule out any 'reversible factors' (e.g. poor palliation, depression, poverty, ill-education, isolation) that may be hindering authentic choice
- Government of Canada – Services and Information for End-of-Life Care:
  - https://www.canada.ca/en/health-canada/topics/end-life-care.html
  - options and decision making at end of life: palliative care, Do Not Resuscitate orders, refusal or withdrawal of treatment, refusal of food and drink, palliative sedation, MAID
  - decisions at end of life: capacity for informed consent, SDM, advanced care planning (written plan, will, or medical directive) often established through a family meeting

MAID: Ethically Appropriate Actions

Respect capable decisions to forgo available treatment options and/or palliative care options

Provide appropriate palliative measures with patient consent

Try to assess reasons for MAID requests to see if there are 'reversible factors' that are directly and unduly influencing one's desire to receive MAID (e.g. depression, pain, loneliness, anxiety) that can be treated

Exploring the Experience of Supporting a Loved One through a Medically Assisted Death in Canada

Can Fam Physician. 2018;64(9):e387-e393

Purpose: To explore the experience of family and close friends of patients seeking MAID in Canada.

Methods: Primary support givers of clinic patients seeking MAID were identified during consultations for an assisted death evaluation. The identified support givers were then invited to participate in the study, and those interested were asked to contact interviewers. Semi-structured interviews were conducted, transcribed, coded, and subjected to content analysis to elucidate common themes.

Results: 18 support people for patients seeking MAID were interviewed. All participants were supportive of their loved one's wishes for MAID and provided emotional and practical support in preparation for the procedure. Some participants reported feeling opposed, however, changed their minds after seeing the suffering their loved ones had to endure. The time before the procedure involved saying goodbye and ceremonial rituals. Those interviewed after the procedure found the death peaceful and reported that it offered advantages compared with natural death in their loved one's individual circumstances.

Conclusion: Participants were supportive of their loved one's wishes for assistance in death to end suffering and found the process to be peaceful overall.

Physician Responsibilities Regarding Death

- physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence
  - Coroner's Act, 1990 (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
  - due to violence, negligence, misconduct, misadventure, or malpractice
  - during pregnancy or is attributable to pregnancy
  - suddenly and unexpectedly
  - from disease which was not treated by a legally qualified medical practitioner
  - from any cause other than disease
  - under suspicious circumstances
  - death from MAID
- coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
- in consultation with forensic pathologists and other specialists, the coroner establishes:
  - the identity of the deceased
  - where and when the death occurred
  - the medical cause of death
  - the means of death (i.e. natural, accidental, suicide, homicide, or undetermined)
- coroners do not make decisions regarding criminality or legal responsibility
- while the Supreme Court of Canada noted that nothing in the Carter v. Canada decision compelled a physician to participate in MAID, the College of Physicians and Surgeons of Ontario mandatory referral policy, which has been upheld by the courts, requires physicians in Ontario to provide an effective referral if the physician conscientiously objects to MAID
  - the impact of MAID on religious institutions' obligation towards patients is not yet clear

Notify coroner if death occurs due to:
Violence, negligence, misconduct
Pregnancy
Sudden or unexpected causes
Disease not treated
Cause other than disease
Suspicious circumstances
MAID

Physician Competence and Professional Conduct

CanMEDS Competencies (Ethical/Policy Statement)

- a framework of professional competencies established by the Medical Council of Canada (MCC) as objectives for the MCC Qualifying Exam
- further information on Medical Council of Canada objectives can be found at www.mcc.ca

Legal Considerations

- physicians' conduct and competence are legally regulated to protect patients and society via mandatory membership to provincial governing bodies (e.g. the CPSO)
- physicians are legally required to maintain a license with the appropriate authority, and are thus legally bound to outlined policies on matters of conduct within their medical practice
- the ultimate constraint on physician behaviour with regards to unprofessionalism is 'conduct unbecoming a physician,' such as inappropriate behaviour with colleagues, conflicts of interest, untruthfulness, unethical billing practices, and sexual impropriety with patients

Common Policies on Physician Conduct

- physicians must ensure that patients have knowledge of/access to on-call coverage and are never abandoned
  - physicians are required to comply with the law, including human rights laws
- sexual conduct with patients, even when consented to by the patient can lead to accusations of battery and professional misconduct by the provincial governing body. Important notes on this topic include:
  - inappropriate sexual conduct includes intercourse, undue touching, inappropriate and unrelated references to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
  - in specific situations, physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact
  - physicians are permanently prohibited from personal relationships with patients whom they saw for psychotherapy
  - in Ontario, physicians must report any colleagues of whom they have information regarding sexual impropriety (as per CPSO Policy on Boundary Violations)
- physicians must maintain adequate records for each patient, which include:
  - demonstration that care has been continuous and comprehensive
  - minimal standards for record-keeping, including readability, diagnosis, differential diagnosis, appropriate tests and referrals, and a coherent patient record, including drugs, a cumulative patient profile, and all aspects of charting that are required for safe patient care (full standards available at www.cpso.on.ca). Another physician should be able to take over the safe care of the patient based on the record
  - records stored for 10 yr in most jurisdictions, though this ought to be verified with one's provincial governing bodies
  - although the medical record is the property of the physician or an institution:
    - the patient or the patient's delegate must be allowed full access to information in the medical record

CPSO Policy: Treating Self and Family Members
Physicians will not diagnose or treat themselves or family members except for minor conditions or in emergencies, and only if no other physician is readily available

CPSO Policy: Ending the Physician-Patient Relationship
Discontinuing services that are needed is an act of professional misconduct
Exceptions include patient request, alternative services arranged, or adequate notice has been given

CMA Code of Ethics
Report any unprofessional conduct by colleagues to the appropriate authority

CanMEDS Competencies
- Communicator

Collaborator
Health Advocate
Leader
Professional
Scholar
Medical Expert

- the patient or delegate must obtain access within a reasonable period of time, usually upon a written request
- the physician can charge a reasonable fee for this service

- in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain hospital records

Research Ethics

- involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
  - study participants are protected
  - study participants are treated in accordance with relevant research ethics norms, including but not limited to: respect for persons, concern for welfare, and justice
  - clinical research is conducted to serve the interests of the participants and/or society as a whole
- the protection of research participants is of the utmost importance when conducting clinical research
- a Research Ethics Board (REB) is responsible for reviewing and approving proposed human research. REB approval is required prior to commencing a research study involving humans
- an ethical dilemma arises for physician researchers when their obligation to patients as their physician comes into conflict with research obligations and/or incentives as a researcher. Physicians pursuing research should not be the primary point of contact responsible for recruiting and consenting their own patients due to the possibility of therapeutic misconception and/or feelings of undue influence/lack of voluntariness
- REB offices located within hospitals may have requirements about who can/cannot recruit and/or consent patients for their possible participation in research
- the Human Research Standards Organization (HRSO) develops and publishes national standards for those interested in overseeing, conducting, and/or participating in human research activities in Canada. All published national standards can be accessed here: https://www.hrso-onrh.org
- in order to become aware of all relevant research ethics principles and norms, of which there are many (the above-mentioned principles and norms are far from an exhaustive list), it is recommended that you read Declaration of Helsinki, the Belmont Report, and complete the Tri-Council Policy Statement: Ethical Conduct on Research Involving Human Subjects (TCPS2) online training. The TCPS 2 (2022) can be accessed here: Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2022) (ethics.gc.ca)

Ethics on Research with Indigenous People

- the Ownership, Control, Access, and Possession (OCAP) principles are "a set of standards that establish important ground rules about how Indigenous peoples' data should be collected, protected, used, or shared"
- OCAP principles are:
  - control: Indigenous peoples, their communities, and representatives have the right to control all aspects of "research and information management processes that impact them"
  - access: "Indigenous peoples must have access to information and data about themselves and their communities regardless of where it is held"
  - possession: Indigenous peoples are stewards of the data. As they possess the data, it is within their jurisdiction and control
- researchers working with Indigenous communities are expected to uphold OCAP principles in their research
- First Nations, Inuit, and Métis (FNIM) communities are self-determining, and as such, may have their own version of OCAP. Investigators should respect each community's autonomy with respect to research, data collection, analysis, interpretation, and knowledge transfer
- Chapter 9 of the TCPS2 discusses and provides considerations regarding research involving FNIM Peoples of Canada. This chapter can be accessed here: Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2022) – Chapter 9: Research Involving the First Nations, Inuit and Métis Peoples of Canada (ethics.gc.ca)

The First Nations Principles of OCAP® [Internet]. Akwesasne (ON): First Nations Information Governance Centre (FNIGC); 2020 [cited 2020 Apr 12]. Available from: www.FNIGC.ca/OCAP. OCAP® is a registered trademark of the First Nations Information Governance Centre (FNIGC)

Guiding Principles for Research Ethics
There are a number of principles that are important to research ethics – the three listed are primary ones that are typically cited, but this list is non-exhaustive.

Respect for persons: informed consent

Beneficence: harm vs. benefit

Justice: avoid exploitation/unjustified exclusion criteria

Informed Consent for Research
- Purpose of study
- Expectations of the research participant
- Name and probability of harm and benefits
  - Whether and/or how participants can withdraw their consent to participate
  - Confidentiality (e.g. how will it be maintained? Are participants going to be deidentified and anonymized?)
  - Privacy (e.g. for how long will participants' data be stored?)
- Nature of physician's participation including compensation

Proposals for research must be submitted to a Research Ethics Board (REB)

Physician-Industry Relations

- healthcare delivery in Canada involves collaboration between physicians and the pharmaceutical and healthcare supply industries in the areas of research, education, and clinical evaluation packages (e.g. product samples)
- however, unlike physicians, pharmaceutical and healthcare supply industries do not have a fiduciary duty to patients and are profit-driven. There exists a motive for pharmaceutical companies, which extends beyond your responsibility as a physician
  - literature is clear that our decision-making is influenced by items such as gifts provided by the pharmaceutical and healthcare supply industries (e.g. pens with brand names inscribed, free lunch and learn sessions)
  - accepting such offers (e.g. saying "yes" to a lunch and learn session being offered by a pharmaceutical company, personal injury law firm, etc.) can directly influence physician practices and beliefs in favour of such promoted products. This influence can result in, for instance, the prescription of medications for reasons other than their efficacy and safety profile, recommending particular law firms to patients (which is outside of one's scope)
  - ultimately, there is a reason as to why the pharmaceutical and healthcare supply industries spend money to build relationships (namely, to influence decision-making in favour of the company)
  - the dissemination of free product samples by pharmaceutical companies is associated with increased patient preference for new drugs that are often more expensive, thus incurring a greater long-term cost for patients and the healthcare system
  - new pharmaceutical products are not always more effective than previous standard of care and may have less robust safety evidence by virtue of being new
- physicians must ensure that their participation in any collaborative efforts with pharmaceutical and healthcare supply industries is in keeping with their duties to their patients and society; however, physicians often struggle to properly identify situations in which a conflict of interest is present. It is recommended that clinicians who want support in identifying and navigating potential conflicts of interest gain bioethics support
- gifts or free products from the pharmaceutical industry are usually inappropriate:
  - sponsorship for travel and fees for conference attendance may be accepted only where the physician is a conference presenter and not just in attendance
  - physicians receiving such sponsorship must disclose this at presentations and/or in written articles; it is important to note, however, that the disclosure of conflicts does not eliminate the potential influence that the conflict may have on physician behaviours

CMA and CPSO Guidelines for Ethically Appropriate Physician-Industry Relations

The primary goal should be the advancement of the health of Canadians

Relationships should be guided by the CMA Code of Ethics

The physician's primary obligation is to the patient

Physicians should avoid any self-interest in their prescribing and referral practices

Physicians should always maintain professional autonomy, independence, and commitment to the scientific method

Resource Allocation

- **definition**: the distribution of any resource to programs and people (e.g. goods and services)
- if healthcare resources are clinically indicated, physicians must make such resources available to patients in a manner that takes into consideration equity, potential biases, and possible discriminatory motivation of offering/not offering such resources
  - a person's and/or society's need for and benefit of certain resources are morally relevant criteria for determining allocation, particularly if resources are scarce
  - gender identity, sex, sexual orientation, religion, level of education, socioeconomic status, or age alone are morally irrelevant criteria in and of themselves (i.e. one must not prevent a patient from accessing a scarce resource exclusively on the basis of age)
  - factors determining whether and/or how resources ought to be allocated must be balanced against each other and weighed on a case-by-case, situation-by-situation basis. For instance, there may be some cases where one's age is relevant to determining how much a patient is expected to/not to benefit from a particular resource, but in other cases, age may be entirely irrelevant
- ethical dilemmas that may arise when deciding how best to allocate scarce resources:
  - favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
  - aggregation problem: providing modest benefits to many individuals vs. significant benefits to few individuals
  - decision-making framework considerations: when to rely on a fair democratic process to arrive at a decision, what does a 'fair' process look like?

Choosing Wisely Canada is the national voice for reducing unnecessary tests and treatments in healthcare. Refer to https://choosingwiselycanada.org/recommendations/ for a comprehensive list of recommendations to assist in decision making as healthcare stewards

Guidelines for Appropriately Allocating Resources

- protect and promote the welfare and best interests of patients
- enable informed, autonomous, and voluntary decision-making
- choose interventions known to be beneficial based on evidence of efficacy
- seek the test(s) or treatment(s) that will be most likely to accomplish the diagnostic or therapeutic goal with minimal expected harms
- advocate for one's patients, but do not manipulate the system to gain unfair advantage
- resolve conflicting claims for scarce resources justly and equitably, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures. Consult with external resources (e.g. bioethics team) to help reduce potential biases in decision-making processes
- if appropriate, sensitively inform patients of the impact of cost constraints on care/the healthcare system
- seek resolution of unacceptable shortages at the level of hospital management or government

Conscientious Objection

Patients Refusing Treatment

- in accordance with the principle of autonomy, it is generally acceptable for capable patients to make an informed decision to refuse medical interventions, although exceptions may occur
- it is important to determine justification for refusal of recommended treatment, to ensure decision-making is informed, etc., particularly if the risks of such refusal are significant
- if SDMs make decisions that are not in the best interests (or, if known, previously expressed wishes) of an incapable child, physicians may have grounds for administering treatment, depending on the acuity of the clinical situation. It is best to consult with Legal Counsel, Bioethics, and one's College if you are considering the administration of treatment without consent since applications to gain this permission (via the Consent and Capacity Board in Ontario, for instance) may be essential
  - in high-acuity scenarios (e.g. refusing blood transfusion based on religious grounds for a child in hemorrhagic shock), physicians have a stronger obligation to act in the child's best interests
  - in lower acuity scenarios (e.g. refusing childhood immunization in a developed nation), there is a stronger obligation to respect the autonomy of the decision-makers

Physicians Refusing to Provide Treatment

- it is the case that with justification provided, physicians may refuse to provide a desired treatment (e.g. a treatment that is not clinically indicated and may cause harm) and/or discharge/discontinue relationships with patients (e.g. if there is no therapeutic relationship or trust due to a series of conflicts), but must ensure these patients can access services elsewhere by way of referring the patient to an available and willing practitioner

Implicit Bias

- implicit bias involves: implicit attitudes, thoughts, and/or feelings that may exist outside of conscious awareness and are therefore difficult to acknowledge and control
  - there exist various types of (implicit) biases (e.g. related to age, race, sex, sexual orientation, gender identity, and socioeconomic circumstances among many other factors)
  - negative attitudes towards certain patients based on implicit biases may contribute to disparities in quality of healthcare received
  - these negative attitudes caused by implicit biases reflect constant pervasive exposure to stereotypical portrayals of members of different "social groups"
- bias and stereotypes can be lethal
  - on September 21, 2008, Brian Sinclair, an Indigenous man, presented to a Winnipeg emergency department with a blocked catheter. His presence was not recorded by triage
  - while he waited in the emergency department waiting room, he lost consciousness, but was not checked on by healthcare staff
  - after being in the waiting room for 34 h, he passed away without having received any medical attention
  - later, an inquest found that healthcare staff thought he was intoxicated or homeless
  - a Manitoba court stated that Brian Sinclair's race, and consequently the stereotypes staff held leading to the assumption that he was intoxicated, were relevant factors in his tragic and preventable death

Suggestions for Noticing Implicit Bias

- before a clinical encounter, physicians are advised to check-in with themselves
- physicians may want to ask themselves:
  - how are they feeling?
  - what are they worried about?
  - what do they notice in their body?
  - what is their intention for the interaction?
  - what do they need to feel more grounded and supported before going into the clinical space?
  - how can they leave some of their assumptions and fears in the hall, instead of bringing them into the examination room?

Working with Vaccine-Hesitant Parents: An Update
Canadian Paediatric Society 2018

1. Understanding the health provider's key role in parental decision-making and not dismissing vaccine refusers from practice
2. Using presumptive and motivational interviewing techniques to identify specific vaccine concerns
3. Using effective and clear language to present evidence for disease risks and vaccine benefits fairly and accurately
4. Managing pain during immunization
5. Reinforcing the importance of parental responsibility for community protection

Clinical Informatics and Ethical Considerations

Key Terms

Health Informatics
- is the study of information design and use in healthcare

Clinical Informatics
- is the application of health informatics knowledge in the clinical setting to promote quality care. It has three domains: collection of longitudinal personal health information for direct patient care, exchange of health information between services and locations, and aggregation of health data for analysis using analytics, artificial intelligence, and machine learning

Digital Health
- is the use of information technology and electronic communication tools, services, and processes to deliver healthcare services

Overview of Digital Health Technologies

Table 6. Overview of Digital Health Technologies and Relevant Ethical Considerations

Digital Health Technologies	Definitions	Ethical Considerations
EMR (Electronic Medical Record)	System of electronically stored patient health information in a digital format	Impact of threats to healthcare information Privacy and confidentiality Security breaches System implementation Data entry inaccuracies
EHR (Electronic Health Record)	Digital collection of medical information (e.g. patient's health history, allergies, immunizations, treatment plans	
LIS (Laboratory Information System)	Computer software that processes, stores, and manages data from all stages of medical processes and tests	
PACS (Picture Archiving and Communication System)	Computer software providing storage and access to images from multiple modalities	

Indigenous Health

Overview of the History and Impact of Colonialism

- the Indigenous health crisis that exists today is a result of many factors, including the impact of colonial laws, oppression, and genocide
- Indigenous health is deeply connected to the land and freedom that have been systematically stolen from its people
- physicians can consider how oppressive legislation plays a role in precluding many Indigenous patients from experiencing health
- you might find this timeline outlining "Key Moments in Indigenous History" helpful: http://education.historicacanada.ca/files/426/Key_Moments_in_Indigenous_History_Timeline.pdf

- long before the arrival of European newcomers, Indigenous peoples lived on and cared for Turtle Island (now known as North America). This history is richly steeped in culture, relationships, and a holistic worldview. The Indigenous peoples had a flourishing trade, complex social and legal systems, and scientific knowledge about astronomy, ecology, agriculture, and medicine. Despite hundreds of years of adversity, Indigenous peoples and their rich cultures persist and thrive today – an indication of the resilience and tenacity of Indigenous peoples and communities

- upon European arrival, Indigenous and non-Indigenous people formed friendships based on mutual respect. These relationships were formalized through treaties. Treaties provided a framework for relationships and the sharing of Indigenous lands in a peaceful and respectful way

- one example of how treaties were documented and enacted was through wampum belts. Wampum belts are intricate visual displays made from clam shells. These belts serve as a living record of agreements. The two-row wampum belt is particularly important for understanding the relationship between Indigenous peoples and Europeans

- in 1613, Kanienkehaka (Mohawk) peoples noticed that settlers were using and living on their traditional lands. The Haudenosaunee Confederation met and discussed how they could live and work together peacefully on the land. Through these discussions, they learned much about one another and the two-row wampum was created: "In one row is a ship with our White Brothers' ways; in the other a canoe with our ways. Each will travel down the river of life side by side. Neither will attempt to steer the other's vessel." This wampum represented three principles: friendship, peace, and the concept of forever
- soon after these treaties were forged, greed and colonial policies began to erode these relationships.
- the treaties and the rights they established with Indigenous peoples became an inconvenience to the expanding European empire, and consequently, they began to be ignored, as they continue to be today
- the Doctrine of Discovery was the piece of colonial law that let European explorers 'discover' lands previously occupied for thousands of years. This doctrine arose from a series of statements from the Pope, which morally and legally justified the dispossession of lands from their Indigenous inhabitants (Terra Nullius)
- this justification is based erroneously on the supposed 'inferiority' of Indigenous peoples to their 'superior' European counterparts. This allowed monarchs to exploit North American land and resources regardless of its original caretakers and use the power of this doctrine to extinguish Indigenous rights. This doctrine continues to have devastating impacts on Indigenous peoples in Canada

Figure 3. Image of a two row wampum belt. It represents friendship, peace, and the concept of forever
Bonaparte D. The Two Row Wampum Belt: An Akwesasne Tradition of the Vessel and Canoe [Internet]. [place unknown]: The People's Voice. 2005 Aug 5 [cited 2020 Apr 16]. Available from: http://www.wampumchronicles.com/tworowwampumbelt.html

- in 1763, King George III issued the *Royal Proclamation* that delineated the process of British settlement of Indigenous lands. This proclamation gave ownership of North America to King George III; however, it stated that Indigenous title existed and would continue to exist. Therefore, any land would belong to the Indigenous people unless otherwise noted and agreed upon in a treaty. This prevented European settlers from taking possession of land that was occupied by Indigenous peoples, unless already purchased by the Crown
- this document unequivocally recognizes Indigenous rights, title, and self-determination. To this day, no law has overruled the Royal Proclamation; therefore, it is still valid according to Canadian law. Additionally, the notion of Indigenous rights is protected in section 25 of the Constitution Act. Although Indigenous rights cannot be legally diminished or extinguished, the Canadian government frequently disregards this fact

- in 1764, the year following the *Royal Proclamation*, the *Treaty of Niagara* would lay the foundation for the relationship between the Crown and First Nations and their coexistence on Turtle Island. At this instance, the Silver Covenant Chain of Friendship was affirmed and both Indigenous and British sovereignty were recognized. The Treaty of Niagara established a multinational familial relationship between the Crown and the Indigenous nations
- over 2000 Indigenous dignitaries, representatives of 24 Indigenous nations across Turtle Island, were present, and the 24-nation wampum belt was created. This wampum represents the relationship between the Indigenous nations and the Crown

- the *British North America (BNA) Act* of 1867 (later renamed the *Constitution Act*, 1982) gave the Canadian government control over "Indians" (notably excluding Inuit and Métis peoples). This act included New Brunswick, Nova Scotia, Ontario, and Québec as a new self-governing federation. This laid the foundation for Canada's laws and governance and the rights of those living in the territory now defined as Canada. The BNA Act stated that the federal government had jurisdiction over "Indians and lands reserved for Indians." Indigenous peoples were not involved in conversations or proceedings associated with the passing of this act

- in 1857, *An Act for the Gradual Civilization of the Indian Tribes in Canada* passed and later absorbed under the larger umbrella of the *Indian Act*
- "it is desirable to encourage the progress of Civilization among the Indian Tribes in this Province, and the gradual removal of all legal distinctions between them and Her Majesty's other Canadian Subjects, and to facilitate the acquisition of property and of the rights accompanying it, by such Individual Members of the said Tribes as shall be found to desire such encouragement and to have deserved it"

- this act encouraged the voluntary enfranchisement of Indigenous people. Enfranchisement is the legal process of exterminating one's "Indian" status and ancestral rights in order to gain Canadian citizenship. Later, involuntary enfranchisement would be enforced. This would extinguish the status of any Indigenous person who served in the armed forces, received a university degree, or became a professional (e.g. lawyer, engineer, physician)

- this act depicts the deliberate intentions of Canadian parliament to erase Indigenous culture and diversity from Canada. Other assimilatory programs such as residential schools, the Sixties Scoop, and Indian hospitals have been implemented over various time periods since Confederation. These policies have created irreparable harm, and much of the poverty and current physical and mental health crises facing Indigenous communities today can be traced back to these colonial injustices, as well as ongoing colonialist policies
- a strong understanding of these historical factors can equip physicians to provide better care and cultivate a more empathetic physician-patient relationship

- the *Indian Act* (1876) allows the Canadian government to obtain complete control over First Nations, status, and reserves. It precluded equal political and economic participation and actually made cultural and spiritual practices illegal

- the *Indian Act* still exists today but has morphed significantly since its establishment. This act has taken total political control, imposed foreign governmental structures (band councils), and eliminated the rights of Indigenous peoples to practice their sacred cultural and spiritual beliefs. Indian agents were government workers who enforced these laws and were given the power to prevent Indigenous peoples from leaving their communities. In 1887, Sir John A. MacDonald stated, "The great aim of our legislation has been to do away with the tribal system and assimilate the Indian people in all respects with other inhabitants of the Dominion as speedily as they are fit to change"

- in terms of health, the *Indian Act* gives the Governor in Council control over the decisions made surrounding regulations of public health and treatment. However, this act does not present any obligation of the Canadian government to provide health services for Indigenous peoples

- Section 141 of the *Indian Act* prevented Indigenous peoples from gathering and discussing their rights or hiring legal representation to fight against this oppression

- Judge Alfred Scow describes the impact that this has had on his peoples: "This provision of the Indian Act was in place for close to 75 years and what that did was it prevented the passing down of our oral history. It prevented the passing down of our values. It meant an interruption of the respected forms of government that we used to have, and we did have forms of government be they oral and not in writing before any of the Europeans came to this country. We had a system that worked for us. We respected each other. We had ways of dealing with disputes"

- in 1951, some amendments were made to the *Indian Act*. The more oppressive sections were amended or erased, such as the outlawing of sacred practices, the inability to leave reserve without permission of an Indian agent, the inability to hire legal counsel, and the inability of Indigenous women to vote in Band Council elections
- the *Indian Act* continued to oppress Indigenous women uniquely by taking away their status if they married a non-Indigenous man. This means that a woman would have to leave her family and community, and consequently lose her treaty and health benefits, including her right to be buried on reserve with her ancestors. The opposite held true for Indigenous men, as it allowed for non-Indigenous women to gain Indian status through marriage

- in the 1970s-80s, Indigenous women began lobbying for equal rights and *Bill C-31* was passed that nullified this law, allowing many women to regain status. However, this law continues to pose significant controversy as this status is only allowed to be passed down to one generation

- Indian status is defined under section 6 of the *Indian Act* and denotes who qualifies and therefore becomes a ward of the government. This is a paternalistic legal relationship that creates two categories of First Nations status
  - 6(1): this person can pass on their status to their children regardless of their partner's heritage
  - 6(2): this person can only pass on their status if their partner is also Indigenous

- this idea of status complicates the identities of many Indigenous peoples (including non-status First Nations, Métis, and Inuit peoples who do not fall under the *Indian Act*) who are prevented from registering and therefore lose government support, their treaty, and health benefits. They also lose their ability to:
  - participate in community politics
  - partake in land claims
  - connect to their ancestral lands

- this displacement and the misconception that non-status peoples are "less Indian" is extremely harmful and often serves as a platform for lateral violence. In this context, lateral violence refers to when a member of an oppressed group behaves in a malicious or violent manner towards another member of that same oppressed group or in a lower position of power. Lateral violence can be traced back to the impact of colonialism

- Indigenous individuals are generally subject to full taxation, though individuals with status are eligible for select tax exemptions through section 87 of the *Indian Act*. It is a pervasive and harmful myth that Indigenous individuals do not pay taxes. For the most part, exemptions only apply to financial matters located on-reserve, with complex and specific criteria to be met. Matters located off-reserve are generally taxed in full. A summary of this is available in Bob Joseph's "Dispelling Common Myths about Indigenous Peoples" https://www.ictinc.ca/hubfs/ebooks/ebooks%202019/Common%20Myths%20eBook%20July%202019.pdf

- the *Indian Act* is a controversial piece of legislature because it undermines the nationhood and sovereignty of Indigenous peoples. However, it is important to understand the Indian Act because it also provides the basis for the historical and constitutional relationship between Indigenous peoples and the Canadian government. Therefore, it cannot be easily removed without having significant ramifications

Movement Towards Reconciliation

- in 1991, the Royal Commission on Aboriginal Peoples (RCAP) was formed to address the inequities that exist, and to work to repair the relationship between Indigenous peoples and Canada. This commission was brought about after the Oka Crisis. The Oka crisis (The Mohawk Resistance) arose from a long-standing history of rejection and ignoring of Indigenous land rights by the Canadian government, and resulted in a 78-day protest of a proposed golf course expansion onto sacred Mohawk territory. The RCAP report (1996) detailed extensive research and recommendations needed to heal and restructure the relationship between Indigenous and non-Indigenous peoples. The majority of these recommendations have not been implemented and there continues to be little government interest in the constitutional issues that affect Indigenous peoples and communities

- in 2008, the Prime Minister of Canada apologized to all those who were affected by the residential school system, where Indigenous children were forced into abusive schools (see Public Health and Preventive Medicine, *Colonization and Healthcare*, PH7). The Truth and Reconciliation Commission was born out of a settlement agreement between the government and residential school survivors. The mission of this commission is to learn and tell the stories of those who attended these schools. This commission hopes to bring about renewed relationships and healing based on mutual understanding and respect. To achieve this goal, the commission put out 94 Calls to Action aiming to bring us closer to reconciliation. These calls urge all levels of the Government of Canada to work together to address systemic inequities by changing policies and programs that continue to oppress Indigenous peoples. Under the category of health, the following recommendations are quoted below:
  - we call upon the federal, provincial, territorial, and Aboriginal governments to acknowledge that the current state of Aboriginal health in Canada is a direct result of previous Canadian government policies, including residential schools, and to recognize and implement the healthcare rights of Aboriginal people as identified in international law, constitutional law, and under the Treaties
  - we call upon the federal government, in consultation with Aboriginal peoples, to establish measurable goals to identify and close the gaps in health outcomes between Aboriginal and non-Aboriginal communities, and to publish annual progress reports and assess long-term trends. Such efforts would focus on indicators such as: infant mortality, maternal health, suicide, mental health, addictions, life expectancy, birth rates, infant and child health issues, chronic diseases, illness and injury incidence, and the availability of appropriate health services
  - in order to address the jurisdictional disputes concerning Aboriginal people who do not reside on reserves, we call upon the federal government to recognize, respect, and address the distinct health needs of the Métis, Inuit, and off-reserve Aboriginal peoples
  - we call upon the federal government to provide sustainable funding for existing and new Aboriginal healing centres to address the physical, mental, emotional, and spiritual harms caused by residential schools, and to ensure that the funding of healing centres in Nunavut and the Northwest Territories is a priority
  - we call upon those who can effect change within the Canadian healthcare system to recognize the value of Aboriginal healing practices and use them in the treatment of Aboriginal patients in collaboration with Aboriginal healers and Elders requested by Aboriginal patients
  - we call upon all levels of government to:
    i. increase the number of Aboriginal professionals working in the healthcare field
    ii. ensure the retention of Aboriginal healthcare providers in Aboriginal communities
    iii. provide cultural competency training for all healthcare professionals
  - we call upon medical and nursing schools in Canada to require all students to take a course dealing with Aboriginal health issues, including the history and legacy of residential schools, the United Nations Declaration on the Rights of Indigenous Peoples, Treaties and Aboriginal rights, and Indigenous teachings and practices. This will require skills-based training in intercultural competency, conflict resolution, human rights, and anti-racism

- going forward as healthcare professionals, we are uniquely responsible for knowing and understanding the impact these historical and legal truths have on our patients. When addressing health inequities that are disproportionately experienced by Indigenous peoples, we need to take into account the impact of 500 years of colonialism. We need to understand how our patients and their ancestors have experienced structural violence and trauma in order to address their physical, mental, emotional, and spiritual health needs. Physicians need to understand that we are all treaty people, and that the above legislation not only applies to Indigenous peoples, but to physicians as well, and all those who benefit from these laws

Indigenous Disproportionate Over-Representation of Biological, Psychological, and Social Co-Morbidities

- physicians may work in various settings in which Indigenous peoples make up a large proportion of the population. Treatment approaches in these settings must consider issues unique to Indigenous peoples, particularly considering that past colonial practices and historical traumas have led to their over-representation in vulnerable groups. Indigenous peoples in Canada have shown great resilience against a long history of colonialism, structural oppression, dispossession, and harmful policies. These historical realities perpetuate current structural barriers that impact the health of Indigenous peoples (see Public Health and Preventive Medicine, *Colonization and Healthcare,* PH7)

- importantly, physicians will encounter Indigenous peoples from a wide variety of personal and historical experiences. Individuals should be invited to share their backgrounds and perspectives if they would like to do so, in an effort to understand the individual's unique context and to endeavour to provide culturally safe care (see *Resources in Indigenous Health, ELOM30*)

Those Receiving Child Welfare Services (The Cycle of Apprehension and the Millennial Scoop)

- similar continuation of the legacies of the residential school systems and the Sixties Scoop, Indigenous families face higher rates of child apprehension currently. In Canada, 52.2% of children (ages 0-14) in foster care are Indigenous, while Indigenous children account for only 7.7% of all Canadian children in this age range (2016)
- 38% of Indigenous children live in poverty compared to 13% of non-Indigenous non-racialized children in Canada (2011)
- in 2016, the Canadian Human Rights Tribunal ruled that the federal government discriminates against First Nations children on reserves by failing to provide the same level of funding for child welfare services that exists for non-Indigenous children, resulting in inequitable services. Despite the ruling recommending compensation, the Tribunal has issued 10 subsequent orders to ensure Canada's compliance. In 2019, the federal government argued the Tribunal was the wrong forum to discuss compensation and suggested there was no evidence of harm to individual children before the Tribunal. The Tribunal rejected both arguments. In September 2019, the Tribunal found that Canada's ongoing discrimination against First Nations children and families was "wilful and reckless" and that it had caused serious pain and suffering for victims of the discrimination. Canada was ordered to pay the maximum amount allowable under the Canadian Human Rights Act to compensate First Nations children, youth, and families who have been harmed by the child welfare system. In October 2019, the federal government launched a court challenge at the Federal Court in an attempt to quash the compensation order, which was subsequently denied
- only once the Tribunal reinforced the initial ruling in December 2019 did the federal government pass an Act respecting First Nations, Inuit, and Métis children, youth, and families, which came into effect in January 2020. This act allows Indigenous communities to exercise jurisdiction in the welfare of their own children over Indigenous Services Canada and provincial or territorial governments. However, the federal government continues to delay compensation and oppose the order for the maximum allowable amount of compensation, despite other federal parties calling on the government to pay

Those in State Custody and the Colonial Legacy Within the Canadian Judicial System

- there is a direct link between family breakdown due to the residential school system, intergenerational trauma and abuse from colonialism, and subsequent higher rates of child apprehension. Interacting with the foster care system and the instability of multiple (sometimes abusive) homes is a predictor of future interaction with the criminal justice system along with poverty and higher unemployment
- 27-30% of adults and 50% of youth taken into custody in 2016-17 were Indigenous, yet Indigenous peoples make up only 4.1% and 8% of Canada's adult and youth populations, respectively
- Indigenous youth are also overrepresented in community supervision
- from 2000 to 2010, the number of incarcerated Indigenous women increased by 86.4%, representing the fastest growing incarcerated population
- Indigenous-based restorative (rather than punitive) justice programs have been proposed to lower recidivism rates for Indigenous offenders

Those with no Fixed Address and the Colonial Legacy of Homelessness

- Toronto's Indigenous population is approximately 2-4x larger than estimates reported by Statistics Canada, as the National Household Survey relies on mailing addresses, and some Indigenous People may be skeptical about providing information to the government given historical and ongoing breaches of trust
- as the statistics significantly underestimate the Indigenous population, resource allocation is severely compromised. More information is available here: http://www.welllivinghouse.com/wp-content/uploads/2022/03/OHC-Toronto-2021-Population-Estimates.pdf
- in Toronto, Indigenous peoples make up roughly 15% of the homeless population, yet only 0.5% of the total population (2010)
- enfranchisement (giving up Indigenous status in order to become a Canadian citizen), on-reserve housing limitations and shortages, dislocation from community and lands in concert with poor government funding and support are important links to Indigenous homelessness today

- attempts to serve the needs of Indigenous people in urban areas include the employment of traditional healers or cultural coordinators in urban health centres as well as the use of traditional medicines (e.g. sage, cedar, sweetgrass, tobacco)

Missing and Murdered Indigenous Women, Girls and Gender Diverse People

- in Canada, Indigenous women and girls are significantly more likely to be murdered or go missing than any other demographic of women
- between 2001 and 2015, homicide rates for Indigenous women were nearly 6 times higher than for non-Indigenous women
- interpersonal violence within Indigenous communities is closely tied to the lasting trauma suffered in the residential school era and has far-reaching health impacts including acute injuries, chronic pain, sexually transmitted infections, unplanned pregnancies, addiction, self-harm, and suicide
- loss of a mother, sister, or daughter also incurs multi-generational trauma on family and family structure in Indigenous communities

Indigenous Health Coverage and Jurisdictions

- policy pertaining to the health of Indigenous peoples is considered to be shared amongst various levels of government, the private sector, and First Nations communities themselves
- this current model relies heavily on state-imposed definitions of Indigenous identity and limits the right to self-determination and self-governance for Indigenous peoples in Canada
- significant historical legislative vagueness, in combination with the multiplicity of authorities involved, creates much variation across provinces and territories, contributing to inequitable distribution of care for Indigenous peoples
- bureaucratic delays in approving and providing care, and jurisdictional debates between authorities over the responsibilities of care, further contribute to a healthcare system which frequently fails to adequately respond to the needs of Indigenous peoples and communities
- the federal government is responsible for the Non-Insured Health Benefits (NIHB) program, which is managed by the First Nations and Inuit Health Branch of Indigenous Services Canada and is based on the Indian Health Policy (1979) and the Health Transfer Policy (1989)
  - the role of the NIHB is to provide eligible First Nations and Inuit individuals with coverage for specific health benefits and services (most predominantly: eye and dental care, pharmacare, transport to and from medical appointments, and mental health counselling). There are very strict criteria to have certain medications and procedures covered
  - the NIHB relies on state-imposed definitions of Indigenous identity; access to the NIHB extends only to individuals who are (1) registered under the Indian Act (and consequently referred to using the paternalistic term "Status Indian"); (2) Inuk, as recognized by the Inuit Land Claim Organization; or (3) a child under 18 months of age whose parent is registered First Nations or recognized Inuk
  - access to care for non-status First Nations and Métis patients is consequently denied under NIHB criteria, despite encountering similar social determinants of health and barriers to healthcare experienced by eligible individuals
  - clients deemed ineligible for NIHB must then rely on provincial or territorial health insurance, social programs, or private insurance plans for healthcare
  - note that NIHB eligibility does not guarantee access to care, as the criteria for approved services is subject to frequent changes and impacted by factors including whether the applicant lives on- or off-reserve
- the Canadian healthcare system must recognize that Indigenous communities are best positioned to identify their own unique health priorities and manage and deliver health care in their communities
  - although there is some development and implementation of Indigenous-led and Indigenous-directed healthcare services in Canada, the effects of colonialist policies and practices continue to perpetuate inequities among Indigenous peoples
  - healthcare providers can work towards dismantling the effects of colonialism in a number of manners, including allyship and advocacy, engaging in cultural safety training, and better educating oneself on Indigenous history, the impact of colonialism, and resources available to meet the unique needs of their patients (see *Resources in Indigenous Health*)
  - British Columbia (BC) has established a First Nations Health Authority as a step in addressing Indigenous self-determination in healthcare

Resources in Indigenous Health

- please consider watching "The Unforgotten," a 36-minute film, which consists of five segments: https://theunforgotten.cma.ca/full-film/
- please consider reviewing this Indigenous Health Guide for Medical Students
  - https://temertymedicine.utoronto.ca/sites/default/files/IndigenousHealthinOntario-compressed.pdf
- the following is a list of fact sheets, reports, and toolkits as well as organizational websites providing resources relating to Indigenous health. All were created by or with Indigenous peoples and organizations unless otherwise stated. These resources share the aim of highlighting Indigenous resilience and promoting strength in Indigenous communities. Though not exhaustive, this list serves as a foundation for the kinds of resources that are available to healthcare providers and/or Indigenous Peoples seeking care. Of note, physicians have a responsibility to become familiar with local or regional services that may be able to provide culturally safe trauma-informed care for Indigenous People

Table 7. Resources in Indigenous Health

	Resource	Ref #
Health Care		
National Collaborating Centre for Indigenous Health (NCCIH)	Extensive database of Indigenous Health research and resources across Canada. Please note that some of these materials may have been collated without Indigenous consultation	1
Canadian Institutes for Health Research (CIHR)	Recommendations in culturally appropriate care for healthcare providers in Canada working with Indigenous peoples, reviewed by the Aboriginal Health Issues Committee	2
Wellesley Institute		
First Peoples, Second Class Treatment: The Role of Racism in the Health and Well-being of Indigenous Peoples in Canada	Report looking in-depth at the relationship between racism, health, and the well-being of Indigenous peoples in Canada	3
First Nations Health Authority (FNAH) (BC)	BC has its own health authority responsible for the planning, delivery, and funding of First Nations Health Programs across the province	4
Indigenous Health Primer produced by the Royal College of Physicians and Surgeons of Canada	An extensive document that discusses anti-racism interventions, trauma-informed care, Indigenous health principles, impact of policies on Indigenous peoples, and the diversity of present Indigenous communities	5
Thunderbird Partnership Foundation	Offers special skills, knowledge, and resources to healthcare workers providing care to First Nations communities. Has particular expertise in providing addiction care	6
Child and Family		
First Nations Child and Family Services (FNCFS)	Interactive map of Canada with all FNCFS service provider locations	7
National Aboriginal Council of Midwives (NACM)	Subset of the larger organization, Canadian Association of Midwives, that provides Indigenous midwives for natal care	8
Indigenous Services Canada	Social programs, such as women's shelters and income assistance in Indigenous communities, funded federally by Indigenous Services Canada	9
Population-Specific		
Inuit Tapiriit Kanatami (ITK)	The national representational body for Inuit people in Canada, with publications on TB elimination strategies and Inuit-specific health literacy resources	10
Patients Facing Additional Layers of Systemic Barriers		
People with no fixed address	Description of Indigenous homelessness from an Indigenous perspective, emphasizing criteria that are not captured in colonial definitions of "homelessness"	11
Indigenous women, girls, and gender diverse people	Multitude of fact sheets published by the Native Women's Association of Canada covering issues such as housing, violence, and health with an intersectional lens	12
	The Final Report of the National Inquiry into Missing and Murdered Indigenous Women and Girls containing testimonies from survivors and Knowledge Keepers, discussion of influencing factors such as intergenerational trauma and insecure housing, as well as 231 calls for justice directed at Canadians and institutions alike	13
Mental health and suicide	The Centre for Suicide Prevention (branch of the Canadian Mental Health Association) offers many Indigenous-specific resources on suicide prevention, life planning, trauma, and cultural sensitivity	14
	Online course called "River of Life," created for people working with Indigenous youth ages 15-24, discusses strategies to strengthen the protective factors of youth at risk of suicide	15
	Trauma-informed Indigenous programs, e.g. Biidaaban Healing Lodge in Ontario and Tsow-Tun Le Lum Society in BC	16, 17
Building Cultural Competency		
University of Alberta's Indigenous Canada online course	Indigenous Canada is a Massive Open Online Course (MOOC) from the Faculty of Native Studies that explores Indigenous histories and contemporary issues in Canada.	18
Cancer Care Ontario, Indigenous Relationship and Cultural Safety Courses	13 courses available to provide knowledge about the history and culture of First Nations, Inuit and Métis people and communities	19

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A Anesthesia

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Acronyms

2,3-BPG	2,3-Bisphosphoglycerate	CVS	cardiovascular system	ITP	immune thrombocytopenic purpura	PCV	pressure-controlled ventilation
ABG	arterial blood gas	CVP	central venous pressure	IV	intravenous	PEEP	positive end-expiratory pressure
ACC	American College of Cardiology	CVD	cardiovascular disease	LA	local anesthetic	PNS	parasympathetic nervous system
ACh	acetylcholine	CXR	chest X-ray	LABA	long-acting β-agonist	PACU	post-anesthetic care unit
AChE	acetylcholinesterase	DIC	disseminated intravascular coagulation	LES	lower esophageal sphincter	PONV	postoperative nausea and vomiting
ACV	assist-control ventilation	DKA	diabetic ketoacidosis	LMA	laryngeal mask airway	PPV	positive pressure ventilation
AFib	atrial fibrillation	DM	diabetes mellitus	LOC	level of consciousness	PVD	peripheral vascular disease
AHA	American Heart Association	$ETCO_2$	end-tidal CO_2	MAC	minimum alveolar concentration	RA	regional anesthesia
ALS	amyotrophic lateral sclerosis	ETT	endotracheal tube	MAP	mean arterial pressure	RSI	rapid sequence induction
aPTT	activated partial thromboplastin time	FiO_2	fraction of oxygen in inspired air	MH	malignant hyperthermia	SABA	short-acting β-agonist
ARDS	acute respiratory distress syndrome	FFP	fresh frozen plasma	MS	multiple sclerosis	SCh	succinylcholine
ASA	American Society of Anesthesiologists	FRC	functional residual capacity	MSK	musculoskeletal	SIADH	syndrome of inappropriate antidiuretic hormone
atm	atmosphere	GA	general anesthesia	NDMR	non-depolarizing muscle relaxant	SNS	sympathetic nervous system
BBB	blood brain barrier	GE	gastroesophageal	NMJ	neuromuscular junction	SV	stroke volume
BMV	bag-mask ventilation	GERD	gastroesophageal reflux disease	NPO	nil per os	SVR	systemic vascular resistance
BP	blood pressure	GI	gastrointestinal	NYHA	New York Heart Association	TIA	transient ischemic attack
CCS	Canadian Cardiovascular Society	GU	genitourinary	OCS	oral corticosteroids	TBW	total body water
CHF	congestive heart failure	Hb(i)	initial hemoglobin	OG	orogastric	TIVA	total intravenous anesthetic
CK	creatine kinase	Hb(f)	final hemoglobin	OR	operating room	TURP	transurethral resection of prostate
CNS	central nervous system	Hct	hematocrit	OSA	obstructive sleep apnea	URTI	upper respiratory tract infection
CO	cardiac output	HES	hydroxyethyl starch	PA	pulmonary artery	V/Q	ventilation/perfusion
CPAP	continuous positive airway pressure	HHS	hyperosmolar hyperglycemic state	$PaCO_2$	arterial partial pressure of carbon dioxide	VT	ventricular tachycardia
CSF	cerebrospinal fluid	HR	heart rate	PaO_2	arterial partial pressure of oxygen	VTE	venous thromboembolism
CV	cardiovascular	ICP	intracranial pressure	PC	patient-controlled		
		ICS	inhaled corticosteroids	PCA	patient-controlled analgesia		
		INR	international normalized ratio				
		IOP	intraocular pressure				

Overview of Anesthesia

- anesthesia: lack of sensation/perception

Preoperative	Preoperative/Intraoperative	Postoperative
Preoperative assessment Patient optimization	Plan anesthetic Pre-medication Airway management Monitors Induction Maintenance Emergence Tracheal extubation	Postoperative care

Difficult Mask Ventilation
Anesth Analg 2009;109(6):1870-1880
Purpose: Define and predict difficult mask ventilation.
Conclusions: Age >55, obesity with BMI >26, history of snoring, beard, lack of teeth, Mallampati III/IV (see *Figure 1, A3*), abnormal mandibular protrusion test, and male gender are all independent risk factors that should be used as predictors for difficult mask ventilation.

Preoperative Assessment

Purpose
- identify concerns for medical and surgical management of patient
- allow for questions to help allay any fears or concerns patient and/or family may have
- arrange further investigations, consultations, and treatments for patients not yet optimized
- plan and consent for anesthetic techniques

History and Physical

History
- age and gender
- indication for surgery
- surgical/anesthetic Hx: previous anesthetics, any complications, previous intubations, and PONV
- FMHx: abnormal anesthetic reactions, MH, and pseudocholinesterase deficiency (see *Uncommon Complications, A29*)
- medications and allergies (see *Preoperative Optimization: Medications, A4*)
- PMHx
  - neurologic: seizures, TIA/strokes, raised ICP, spinal disease, aneurysm, and conditions affecting NMJ (e.g. myasthenia gravis)
  - CVS: angina/CAD, MI, CHF, HTN, valvular disease, dysrhythmias, PVD, conditions requiring endocarditis prophylaxis, exercise tolerance, and CCS/NYHA class (see Cardiology and Cardiac Surgery *sidebar for CCS Classification,* C23and *sidebar for New York Heart Association Classification,* C54)
  - respiratory: smoking, asthma, COPD, recent URTI, and OSA
  - GI: GERD, liver disease, and NPO status
  - renal: acute vs. chronic renal insufficiency, dialysis, and chronic kidney disease
  - hematologic: anemia, coagulopathies, and blood dyscrasias

- MSK: arthritis (e.g. rheumatoid arthritis, scleroderma), cervical spine pathology (e.g. cervical tumours, cervical infections/abscesses, trauma to cervical spine, and previous cervical spine surgery), and cervical spine instability (e.g. trisomy 21)
- endocrine: DM, thyroid disorders, and adrenal disorders
- other: morbid obesity, pregnancy, and ethanol/recreational drug use

Physical Exam

- weight, height, BP, HR, respiratory rate, and O_2 saturation
- focused physical exam of the CNS, CVS, and respiratory systems
- general assessment of nutrition, hydration, and mental status
- airway assessment is done to determine intubation difficulty (no single test is specific or sensitive) and ventilation difficulty
  - cervical spine stability and neck movement – upper cervical spine extension, lower cervical spine flexion ("sniffing" position – see *Figure 6C, A8*)
  - Mallampati classification (see *Figure 1*)
  - "3-3-2 rule" (see *Figure 2*)
    - 3 of patient's own fingers can be placed between the incisors (incisor distance)
    - 3 fingers along the floor of the mandible between the mentum and hyoid bone (hyoid-mental distance)
    - 2 fingers in the superior laryngeal notch (thyroid-hyoid distance)
  - thyromental distance (distance from the mentum to the thyroid notch in midline with neck extended); <3 finger breadths (<6 cm) is associated with difficult intubation
  - anterior jaw subluxation; <1 finger breadth is associated with difficult intubation
- tongue size
- dentition, dental appliances/prosthetic caps, existing chipped/loose teeth – pose aspiration risk if dislodged and patients should be informed of rare possibility of damage
- nasal passage patency (if planning nasotracheal intubation)
- assess potential for difficult ventilation
- examination of anatomical sites relevant to lines and blocks
  - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
  - sites for IV, CVP, and PA catheters

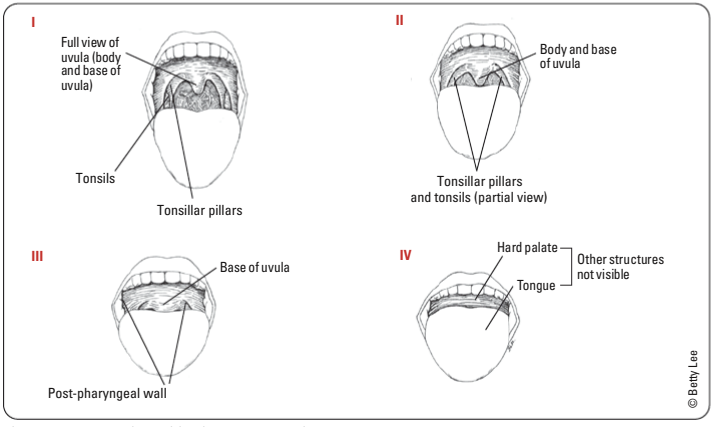

Figure 1. Mallampati classification of oral opening

Evaluation of Difficult Airway

LEMON
Look – obesity, beard, dental/facial abnormalities, neck, facial/neck trauma
Evaluate – 3-3-2 rule
Mallampati score (≥3)
Obstruction – stridor, foreign bodies, masses
Neck mobility

Assessment of Difficult Ventilation Anesthesiology 2000:92:1229-1236

BONES
Beard
Obesity (BMI >26)
No teeth
Elderly (age >55)
Snoring Hx (OSA)

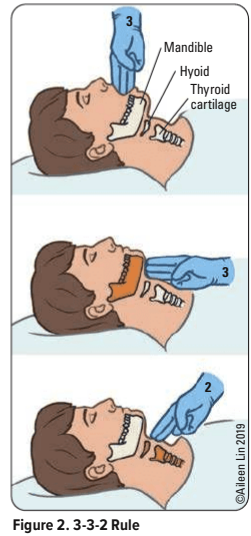

Figure 2. 3-3-2 Rule

Cormack-Lehane Classification of Laryngeal View (*Figure 3, A4*)
Grade 1: all laryngeal structures revealed
Grade 2: posterior laryngeal showing posterior vocal folds and arytenoids
Grade 3: larynx concealed, only epiglottis
Grade 4: neither glottis nor epiglottis

Preoperative Investigations

- routine preoperative investigations are only necessary if there are comorbidities or certain indications

Table 1. Suggested Indications for Specific Investigations in the Preoperative Period

Test	Indications
CBC	Major surgery requiring group and screen or cross and match; chronic CV disease, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression; patient <1 y/oo
Sickle Cell Screen	Genetically predisposed patient (hemoglobin electrophoresis if screen is positive)
INR, aPTT	Anticoagulant therapy, bleeding diathesis, liver disease
Electrolytes and Creatinine	HTN, renal disease, DM, pituitary or adrenal disease; vascular disease, digoxin, diuretic, or other drug therapies affecting electrolytes
Fasting Glucose Level	DM (repeat on day of surgery)
Pregnancy (β-hCG)	Women of reproductive age
ECG	Heart disease, DM, other risk factors for cardiac disease; subarachnoid or intracranial hemorrhage, cerebrovascular accident, head trauma
CXR	Patients with new or worsening respiratory symptoms/signs

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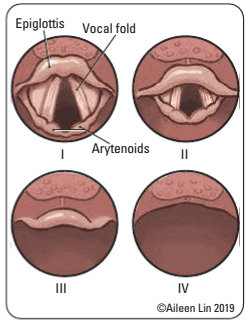


Figure 3. Laryngeal views

American Society of Anesthesiology Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- **ASA 1**: a healthy, fit patient
- **ASA 2:** a patient with mild systemic disease
  - e.g. controlled T2DM, controlled essential HTN, obesity, smoker
- **ASA 3**: a patient with severe systemic disease that limits activity
  - e.g. stable CAD, COPD, DM, obesity
- **ASA 4**: a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure
- **ASA 5**: a moribund patient not expected to survive 24 h without surgery
  - e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- **ASA 6**: declared brain dead, a patient whose organs are being removed for donation purposes
- for emergency operations, add the letter E after classification (e.g. ASA 3E)

Continuation vs. Discontinuation of Antiplatelet Therapy for Bleeding and Ischaemic Events in Adults Undergoing Non-Cardiac Surgery
Cochrane DB Syst Rev 2018; CD012584
Purpose: To compare the effect of continuation vs. discontinuation of antiplatelet therapy on the occurrence of bleeding and ischaemic events in adults undergoing non-cardiac surgery.
Methods: RCTs in Cochrane Central Register of Controlled Trials, MEDLINE, and Embase that compared adults taking single or dual antiplatelet therapy for at least two weeks, including patients with at least one cardiac risk factor. Included general, spinal, and regional anesthesia and excluded minor procedures involving only local anesthetic/sedation.
Results: 5 trials, 666 adult patients. Continuation or discontinuation had no difference on mortality at 30 d postoperative (RR 1.21, 95% CI 0.34-4.27), blood loss (RR 1.37, 95% CI 0.83-2.26), or ischaemic events within 30 d of surgery (RR 0.67, 95% CI 0.25-1.77).
Conclusions: Moderate evidence supporting continuation or discontinuation of antiplatelet therapy makes no difference on bleeding requiring transfusion. Low evidence supporting no difference in mortality or ischaemic events.

Preoperative Optimization

- in general, prior to elective surgery:
  - any fluid and/or electrolyte imbalance should be corrected
  - extent of existing comorbidities should be understood and these conditions should be optimized prior to surgery
  - medications may need adjustment

Medications

- pay particular attention to cardiac and respiratory medications, opioids, and drugs with many side effects and interactions
- **preoperative medications to consider as prophylaxis**
  - risk of GE reflux: antacids (e.g. sodium citrate), H_2 antagonists and/or prokinetic agents (e.g. metoclopramide) 0.5-1 h prior to surgery
  - risk of infective endocarditis, GI/GU interventions: antibiotics
  - risk of adrenal suppression: steroid coverage
  - anxiety: consider benzodiazepines
  - COPD, asthma: bronchodilators
  - CAD risk factors: nitroglycerin and β-blockers
- **preoperative medications to stop prior to surgery**
  - oral antihyperglycemics: do not take on the day of surgery
  - angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB): do not take on the day of surgery (controversial – they increase the risk of hypotension post-induction but have not been shown to increase mortality or adverse outcomes; therefore, some people hold and some do not)
  - warfarin (consider bridging with heparin), antiplatelet agents (e.g. clopidogrel), Xa inhibitor, direct thrombin inhibitors
    - discuss perioperative use of ASA and NSAIDs with surgeon (± patient's cardiologist/internist)

See Landmark Anesthesiology Trials table for more information on the POISE-2 trial, which evaluates low-dose aspirin vs. placebo on the rate of death and major cardiovascular events in patients having noncardiac surgery.

- for patients undergoing non-cardiac surgery, starting or continuing low-dose ASA in the perioperative period does not appear to protect against postoperative MI or death, but increases the risk of major bleeding
  note: this does not apply to patients with bare metal stents or drug-eluting coronary stents
- herbal supplements (e.g. ephedra, garlic, ginkgo, ginseng, kava, St. John's Wort, valerian, echinacea – stop one week prior to elective surgery)

- **preoperative medications to adjust**
  - insulin (consider insulin/dextrose infusion or holding dose), prednisone, bronchodilators

Fasting Guidelines

Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists' Society)

- fasting guidelines should change depending on patients' pre-existing medical conditions. In the case of emergent procedures, consider the risk of delaying surgery against the risk of aspiration
- before elective procedures, the minimum duration of fasting should be:
  - 8 h after a large meal of solids particularly containing protein (e.g. meat) or fatty foods
  - 6 h after a light meal (e.g. non-fatty meal such as toast)
  - 6 h after ingestion of infant formula, non-human milk, or expressed breast milk fortified with additions
  - 4 h after ingestion of breast milk
  - 2 h after clear fluid intake (including water, pulp-free juice, complex carbohydrate beverages, and tea or coffee without milk) for adults
  - 2 h after clear fluid intake for infants and children

Hypertension

- sBP >180 mmHg or dBP >110 mmHg is an independent risk factor for perioperative cardiac events, target below these values
- continue antihypertensive medications up to morning of surgery and resume as soon as possible postoperatively
- assess for end-organ damage and treat accordingly

Coronary Artery Disease

- ACC/AHA Guidelines (2014) recommend that at least 60 d should elapse after a MI before non-cardiac surgery in the absence of a coronary intervention
  - this period carries an increased risk of re-infarction/death
  - if operative procedure is essential and cannot be delayed, then invasive intra- and postoperative ICU monitoring is required to reduce the above risk
- mortality with perioperative MI is 20-50%
- perioperative β-blockers
  - may decrease cardiac events and mortality (but increases risk of perioperative strokes)
  - continue β-blocker if patient is routinely taking it prior to surgery
  - consider initiation of β-blocker in:
    - patients with CAD or indication for β-blocker
    - intermediate or high-risk surgery, especially vascular surgery

Respiratory Diseases

- smoking
  - adverse effects: altered mucus secretion and clearance, decreased small airway calibre, altered O_2 carrying capacity, increased airway reactivity, and altered immune response
  - abstain at least 4-8 wk preoperatively if possible
  - if unable, abstaining even 24 h preoperatively has been shown to increase O_2 availability to tissues
- asthma
  - preoperative management depends on degree of baseline asthma control
  - increased risk of bronchospasm from intubation
  - administration of short course (up to 1 wk) preoperative corticosteroids and inhaled β2-agonists decreases the risk of bronchospasm and does not increase the risk of infection or delay wound healing
  - avoid non-selective β-blockers due to risk of bronchospasm (cardioselective β-blockers (metoprolol, atenolol) do not increase risk in the short-term)
  - delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
  - ideally, delay elective surgery by a minimum of 6 wk if patient develops URTI
- COPD
  - anesthesia, surgery (especially abdominal surgery and upper abdominal surgery, in particular) and pain predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation, and respiratory failure

Perioperative β-blockers for Preventing Surgery-Related Mortality and Morbidity in Adults undergoing Cardiac Surgery
Cochrane DB Syst Rev 2019;9:C.D013435
Purpose: To assess the effectiveness of preoperatively-administered β-blockers for the prevention of surgery-related mortality and morbidity in adults undergoing cardiac surgery.
Conclusions: No evidence of a difference in early all-cause mortality, MI, cerebrovascular events, hypotension, and bradycardia. However, there may be a reduction in AFib and ventricular arrhythmias when β-blockers are used. A larger sample size is likely to increase the certainty of this evidence.

Perioperative β-blockers for Preventing Surgery-Related Mortality and Morbidity in Adults undergoing Non-Cardiac Surgery
Cochrane DB Syst Rev 2019;9:C.D013438
Purpose: Assess effectiveness of preoperatively-administered β-blockers in prevention of surgery-related morbidity and mortality after non-cardiac surgery.
Conclusions: No difference in cerebrovascular events or ventricular arrhythmias. β-blockers may reduce AFib and MI. However, β-blockers may increase bradycardia and probably increase hypotension. Overall low quality and certainty evidence for these findings.

β-blockers

β1-receptors are located primarily in the heart and kidneys

β2-receptors are located in the smooth muscle (i.e. bronchi, uterus)

Non-selective β-blockers block β1 and β2-receptors (labetalol*, carvedilol**, nadolol). Caution is required with non-selective β-blockers, particularly in patients with respiratory conditions where β2 blockade can result in airway reactivity
*labetalol is both an α- and β-blocker
**carvedilol is also both an α- and β-blocker

- preoperative ABG is needed for all COPD stage II and III patients to assess baseline respiratory acidosis and plan postoperative management of hypercapnia
- cancel/delay elective surgery for acute exacerbation

Aspiration

- increased risk of aspiration with:
  - decreased LOC (drugs/alcohol, head injury, CNS pathology, trauma/shock)
  - delayed gastric emptying (non-fasted within 8 h, diabetes, narcotics)
  - decreased sphincter competence (GERD, hiatus hernia, nasogastric tube, pregnancy, obesity)
  - increased intra-abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
  - unprotected airway (LMA and any other supraglottic airway)
- management
  - manage risk factors if possible
  - utilize protected airway (i.e. ETT)
  - reduce gastric volume and acidity
  - delay inhibiting airway reflexes with muscular relaxants
  - employ RSI (see *Rapid Sequence Induction, A16*)

Hematological Disorders

- history of congenital or acquired conditions (sickle cell anemia, factor VIII deficiency, ITP, liver disease)
- evaluate hemoglobin, hematocrit, and coagulation profiles when indicated (see *Table 1, A4*)
- anemia
  - preoperative treatments to increase hemoglobin (PO or IV iron supplementation, erythropoietin, or pre-admission blood collection in certain populations)
- coagulopathies
  - discontinue or modify anticoagulation therapies (warfarin, clopidogrel, ASA, apixaban, dabigatran) in advance of elective surgeries
  - administration of reversal agents if necessary: vitamin K, FFP, prothrombin complex concentrate, recombinant activated factor VII

Endocrine Disorders

- DM
  - clarify type 1 vs. type 2
  - clarify treatment – oral anti-hyperglycemics and/or insulin
  - assess glucose control with history and HbA1c; patients with well-controlled diabetes have more stable glucose levels intraoperatively
  - end organ damage: be aware of damage to cardiovascular and renal, and central, peripheral, and autonomic nervous systems
  - preoperative guidelines for DM:
    - verify target blood glucose concentration with frequent glucose monitoring: <10 mmol/L in critical patients, <7.8 mmol/L in stable patients
    - use insulin therapy to maintain glycemic goals
    - hold biguanides, α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, and GLP-1 agonists on the morning of surgery
    - consider cancelling non-emergency procedures if patient presents with metabolic abnormalities (e.g. DKA, HHS, etc.) or glucose reading above 22.2-27.7 mmol/L
      - formulate intraoperative glucose management plan based on type (1 vs. 2), glucose control, and extent of end organ damage
- hyperthyroidism
  - can experience sudden release of thyroid hormone (i.e. thyroid storm) if not treated or well-controlled preoperatively
  - treatment: β-blockers and preoperative prophylaxis
- adrenocortical insufficiency (e.g. Addison's, exogenous steroid use)
  - consider intraoperative steroid supplementation

Obesity and Obstructive Sleep Apnea

- assess for comorbid conditions and administer testing to characterize the severity, if needed
- severity of OSA may be determined from sleep studies and prescribed pressure settings of home CPAP device

Implementation of a Comprehensive Patient Blood Management Program for Hospitalized Patients at a Large United States Medical Center
Mayo Clin Proc. 2021;96(12):2980
Purpose: To assess changes to utilization of inpatient transfusion and the associated outcomes with implementation of a Patient Blood Management Program.
Methods: An observational study was conducted between 2010 and 2017 at a major US academic centre. Transfusion usage and clinical outcomes were assessed.
Results: 400998 admissions were assessed. Overall usage of inpatient transfusion decreased from 607 to 405 per 1000 admissions. Also, length of stay in hospital and in-hospital adverse events decreased.
Conclusion: This study exhibits that hospital-wide patient blood management protocols result in an overall decrease in transfusion usage and improved clinical outcomes.

Interventions for Preoperative Smoking Cessation
Cochrane DB Syst Rev 2014;3:CD002294
Purpose: Assess the effect of preoperative smoking intervention on smoking cessation at the time of surgery and 12 mo postoperatively, and on the incidence of postoperative complications.
Methods: Systematic review including RCTs that recruited people who smoked prior to surgery, offered a smoking cessation intervention, and measured preoperative and long-term abstinence from smoking or the incidence of postoperative complications or both.
Results: Thirteen trials enrolling 2010 participants included. Overall quality of evidence was moderate. Compared studies involving intensive intervention, which included multi-session face to face counselling or computer-based scheduled interventions, vs. brief interventions. These were pooled separately. An effect on cessation at the time of surgery was apparent in both subgroups, but the effect was larger for intensive intervention. For long term cessation, only the intensive intervention showed effect. In those that had intensive intervention there was significant effect in preventing any postoperative complications.
Conclusion: There is evidence that preoperative smoking interventions providing behavioural support and offering NRT increase short-term smoking cessation and may reduce postoperative morbidity. Interventions that begin 4 to 8 wk before surgery, include weekly counselling, and use NRT are more likely to have an impact on complications and long-term smoking cessation.

Preoperative Anemia and Postoperative Outcomes in Non-Cardiac Surgery: A Retrospective Cohort Study
Lancet 2011;378:1396-1407
Purpose: Assess effect of preoperative anemia on 30 d postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.
Methods: Patients undergoing major non-cardiac surgery in 2008 from the American College of Surgeons' National Surgical Quality Improvement Program database.
Results: 227425 adult patients. Postoperative mortality at 30 d was higher in patients with anemia than those without (OR 1.42, 95% CI 1.31-1.54).
Conclusion: Preoperative anemia, even to a mild degree, is independently associated with an increased risk of 30 d morbidity and mortality.

Monitoring

Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

- an anesthetist present: "the only indispensable monitor"
- a completed preanesthetic checklist: including ASA class, NPO policy, and Hx and investigations
- a perioperative anesthetic record: HR and BP every 5 min, O_2 saturation, $ETCO_2$, dose and route of drugs and fluids
- continuous monitoring: see *Routine Monitors for All Cases*

Routine Monitors for All Cases

- pulse oximeter, BP monitor, ECG, capnography (required for GA and deep procedural sedation, Ramsay Sedation Scale 4-6), and an agent-specific anesthetic gas monitor when inhalational anesthetic agents are used
- the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometry, and manometer to measure ETT cuff pressure

Elements to Monitor

- anesthetic depth
  - end-tidal inhaled anesthetic monitoring and EEG monitoring, such as a Bispectral Index monitor, can be used as assessments of anesthetic depth
  - inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing, or sweating. However, these findings are non-specific
  - excessive: hypotension, bradycardia
- oxygenation: pulse oximetry, FiO_2
- ventilation: verify correct position of ETT, chest excursions, breath sounds, $ETCO_2$ analysis, end-tidal inhaled anesthesia analysis
- circulation: HR, rhythm, BP, telemetry, oximetry, pulmonary capillary wedge pressure
- temperature
- hourly urine output

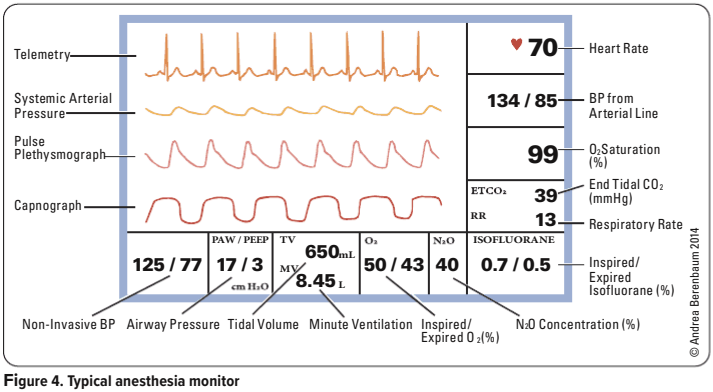


Figure 4. Typical anesthesia monitor

Airway Management

Airway Anatomy

- resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- glottic opening: triangular space formed between the true vocal cords; narrowest segment of the laryngeal opening in adults
  - space through which one visualizes proper placement of the ETT
- trachea begins at the level of the thyroid cartilage, C6, and bifurcates into the right and left main bronchi at T4-T5 (approximately the sternal angle)

Pre-Anesthetic Checklist

MS MAIDS
Machine: connected, pressures okay, all metres functioning, vaporizers full
Suction: connected and working
Monitor: all monitors appropriate for the case
Airway: laryngoscope and blades, ETT, syringe, stylet, oral and nasal airways, tape, bag, and mask
IV: second IV set-up and ready if needed
Drugs: case-specific drugs ready and emergency medications in correct location and accessible
Special equipment: OG tube, CVP monitor, shoulder roll, etc.

Screening for OSA
Br J Anaesth 2012;108:768–775

STOP-BANG
Snoring – loud
Tiredness – day-time
Observed apnea – during sleep
Pressure – HTN
Body mass index – >35
Age – >50 y/o
Neck – large neck circumference (>40 cm)
Gender – male

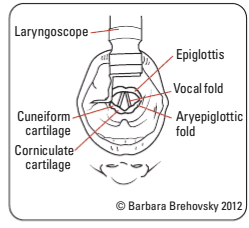


Figure 5. Landmarks for intubation

See Landmark Anesthesiology Trials table for more information on the BAG-RECALL trial, which compares the EEG-derived BIS and end-tidal anesthetic-agent concentration (ETAC) for the prevention of unintended intraoperative awareness in patients at high risk for awareness during surgery.

Will This Patient Be Difficult to Intubate?
JAMA 2019;321:493-503
Purpose: To identify risk factors and physical findings that predict difficult intubation.
Methods: Systematic review of high quality studies (n=62) that evaluate the accuracy of clinical findings for identifying difficult intubation.
Results: Difficult intubation was best predicted by an upper lip bite test (LR 14, 95% CI 9.9 to 22), hyomental distance range <3-5.5 cm (LR 9.4, 95% CI 4.1-10), and a Mallampati score ≥3 (LR 4.1, 95% CI 3.0-5.6). The strongest risk factor for difficult intubation is prior history of difficult intubation.
Conclusion: Although clinical findings are useful for predicting difficult intubation, no clinical finding reliably exclude a difficult intubation.

Methods of Supporting Airways

1. non-definitive airway (patent airway)
   - jaw thrust/chin lift
   - oropharyngeal and nasopharyngeal airway
   - bag mask ventilation
   - LMA
2. definitive airway (patent and protected airway)
   - ETT (oral or nasal)
   - surgical airway (cricothyrotomy or tracheostomy)

Table 2. Methods of Supporting the Airway

	Bag and Mask	LMA	ETT
Advantages/ Indications	Basic Non-invasive Readily available	Easy to insert Less airway trauma/irritation than ETT Frees up hands (vs. face mask) Primarily used in spontaneously ventilating patient	Indications for intubation (5 Ps) **P**atent airway **P**rotects against aspiration **P**ositive pressure ventilation **P**ulmonary toilet (suction) **P**harmacologic administration during hemodynamic instability
Disadvantages/ Contraindications	Risk of aspiration if decreased LOC Cannot ensure airway patency Inability to deliver precise tidal volume Operator fatigue	Risk of gastric aspiration PPV<20 cm H_2O needed Oropharyngeal/retropharyngeal pathology or foreign body Does not protect against laryngospasm or gastric aspiration	Insertion can be difficult Muscle relaxant usually needed Most invasive – see *Complications During Laryngoscopy and Intubation, A9* Supraglottic/glottic pathology that would preclude successful intubation
Other	Facilitate airway patency with jaw thrust and chin lift Can use oropharyngeal/ nasopharyngeal airway	Sizing by body weight (approx.): 40-50 kg: 3 50-70 kg: 4 70-100 kg: 5	Auscultate to avoid endobronchial intubation Sizing (approx.): Male: 8.0-9.0 mm Female: 7.0-8.0 mm Pediatric Uncuffed (age >2 y/o): (age/4) + 4 mm

Tracheal Intubation

Preparing for Intubation

- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare, and assess for potential difficulties (see *Preoperative Assessment, A2*)
- ensure equipment is available and working (test ETT cuff, check laryngoscope light and suction, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% O_2 for 3-5 min or for 4-8 vital capacity breaths
- may need to suction mouth and pharynx first

Proper Positioning for Intubation

- align the three axes (mouth, pharynx, and larynx) to allow visualization from oral cavity to glottis
- "sniffing position": flexion of lower C-spine (C5-C6), bow head forward, and extension of upper C-spine at atlanto-occipital joint (C1), nose in the air (see *Figure 6C*)
  - contraindicated in known/suspected C-spine fracture/instability
  - poor/no view of glottic opening can be remediated by anterior laryngeal pressure
- laryngoscope tip placed in the epiglottic vallecula in order to visualize vocal cords

Equipment for Intubation

MDSOLES
Monitors
Drugs
Suction
Oxygen source and self-inflating bag with oropharyngeal and nasopharyngeal airways
Laryngoscope
ETT (appropriate size and one size smaller)
Stylet, Syringe for tube cuff inflation

Medications that can be given through the ETT

NAVEL
Naloxone
Atropine
Ventolin
Epinephrine
Lidocaine

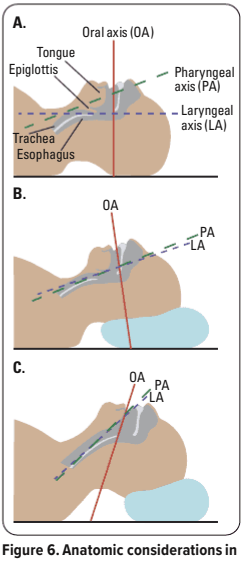


Figure 6. Anatomic considerations in laryngoscopy
A. Neutral position
B. C-spine flexion
C. C-spine flexion with atlanto-occipital extension

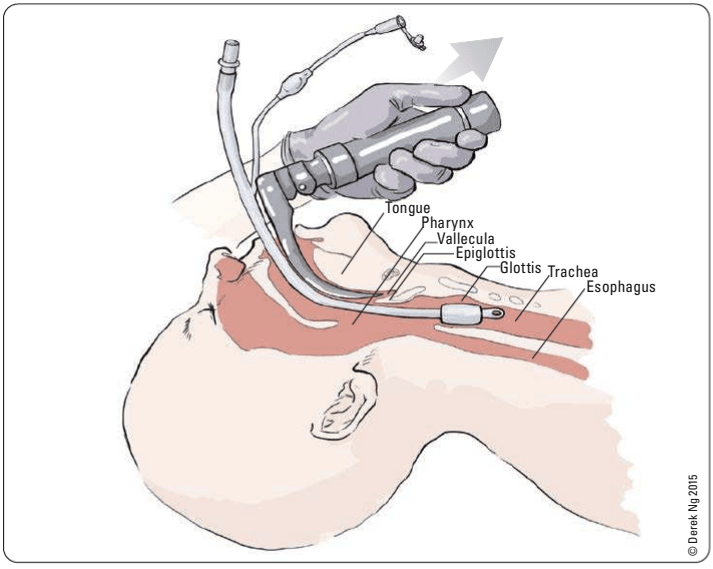


Figure 7. Sagittal view of airway with laryngoscope in vallecula

Tube Insertion

- laryngoscopy and ETT insertion can incite a significant sympathetic response via stimulation of cranial nerves IX and X due to a "foreign body reflex" in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP, and coughing
- a malpositioned ETT is a potential hazard for the intubated patient
  - if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
  - if too shallow, may lead to accidental extubation, vocal cord trauma, or laryngeal paralysis as a result of pressure injury by the ETT cuff
- the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina, and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
- approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women

Differential Diagnosis of Poor Bilateral Breath Sounds after Intubation

DOPE
Displaced ETT
Obstruction
Pneumothorax
Esophageal intubation

Confirmation of Tracheal Placement of Endotracheal Tube

- direct
  - visualization of ETT passing through cords
  - bronchoscopic visualization of ETT in trachea
- indirect
  - $ETCO_2$ in exhaled gas measured by capnography (gold standard for confirming the ETT is in the airway)
  - auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
  - bilateral chest movement, condensation of water vapour in ETT visible during exhalation, and no abdominal distention
  - refilling of reservoir bag during exhalation
  - CXR (rarely done): only confirms the position of the tip of ETT, not its location in the trachea vs. esophagus, but can confirm endobronchial intubation
- esophageal intubation suspected when:
  - $ETCO_2$ zero or near zero on capnograph
  - abnormal sounds during assisted ventilation
  - impairment of chest excursion
  - hypoxia/cyanosis
  - presence of gastric contents in ETT
  - breath sounds heard when auscultating over epigastrium/left upper quadrant
  - distention of stomach/epigastrium with ventilation

Complications During Laryngoscopy and Intubation

- dental damage
- laceration (lips, gums, tongue, pharynx, vallecula, esophagus)
- laryngeal trauma
- esophageal or endobronchial intubation

- accidental extubation
- insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- laryngospasm (see *Extubation, A20, for definition*)
- bronchospasm
- accidental extubation

Difficult Airway

- difficulties with bag-mask ventilation, supraglottic airway, laryngoscopy, passage of ETT through the cords, infraglottic airway, or surgical airway
- algorithms exist for difficult airways (Can J Anesth 2013;60:1119-1138), see *Appendices, A30*
- preoperative assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures
- if difficult airway expected, consider:
  - awake intubation
  - intubating with bronchoscope, fiberoptic laryngoscope, video laryngoscope, etc.
- if intubation unsuccessful after induction:
  1. CALL FOR HELP
  2. ventilate with 100% O_2 via bag and mask
  3. consider returning to spontaneous ventilation and/or waking patient
- if bag and mask ventilation inadequate:
  1. CALL FOR HELP
  2. attempt ventilation with oral airway
  3. consider/attempt LMA
  4. emergency invasive airway access (e.g. surgical or percutaneous airway, jet ventilation, and retrograde intubation)

If you encounter difficulty with tracheal intubation, oxygenation is more important than intubation

Oxygen Therapy

- in general, the goal of O_2 therapy is to maintain arterial O_2 saturation (SaO_2) >90%
- small decrease in saturation below SaO_2 of 90% corresponds to a large drop in PaO_2
- in intubated patients, O_2 is delivered via the ETT
- in patients not intubated, there are many O_2 delivery systems available; the choice depends on O_2 requirements (FiO_2) and the degree to which precise control of delivery is needed

Low Flow Systems

- provide O_2 at flows between 0-10 L/min
- acceptable if tidal volume 300-700 mL, respiratory rate (RR) <25 breaths/min, consistent ventilation pattern
- dilution of O_2 with room air results in a decrease in FiO_2
- an increase in minute ventilation (tidal volume x RR) results in a decrease in FiO_2
- e.g. nasal cannula (prongs)
  - well tolerated if flow rates <5-6 L/min; drying of nasal mucosa at higher flows
  - nasopharynx acts as an anatomic reservoir that collects O^2
  - delivered O_2 concentration (FiO_2) can be estimated by adding 4% for every additional litre of O_2 delivered
  - provides FiO_2 of 24-44% at O_2 flow rates of 1-6 L/min

Reservoir Systems

- use a volume reservoir to accumulate O_2 during exhalation, thus increasing the amount of O_2 available for the next breath
- simple face mask
  - covers patient's nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore O_2 tubing at a rate of at least 6 L/min to ensure that exhaled CO_2 is flushed through the exhalation ports and not rebreathed
  - provides FiO_2 of 55% at O_2 flow rates of 10 L/min
- non-rebreather mask
  - a reservoir bag and a series of one-way valves prevent expired gases from re-entering the bag
  - during the exhalation phase, the bag accumulates with O_2
  - provides FiO_2 of 80% at O_2 flow rates of 10-15 L/min

High Flow Systems

- generate flows of up to 50-60 L/min
- meet/exceed patient's inspiratory flow requirement
- deliver consistent and predictable concentration of O_2
- Venturi mask
  - delivers specific FiO_2 by varying the size of air entrapment
  - O_2 concentration determined by mask's port and NOT the wall flow rate
  - enables control of gas humidity
  - FiO_2 ranges from 24-50%

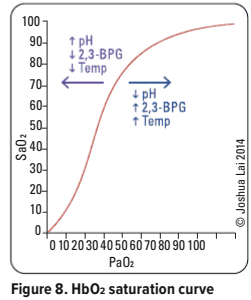


Figure 8. HbO_2 saturation curve

Composition of Air
78.1% nitrogen
20.9% oxygen
0.9% argon
0.04% carbon dioxide

Ventilation

- ventilation is maintained with PPV in patients given muscle relaxants
- assisted or controlled ventilation can also be used to assist spontaneous respirations in patients not given muscle relaxants as an artificial means of supporting ventilation and oxygenation

Mechanical Ventilation

- indications for mechanical ventilation
  - apnea
  - hypoventilation/acute respiratory acidosis
  - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
  - required hyperventilation (to lower ICP)
  - deliver PEEP
  - increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation
  - airway complications
    - tracheal stenosis, laryngeal edema
  - alveolar complications
    - ventilator-induced lung injury (barotrauma, volutrauma, atelectatrauma), ventilator-associated pneumonia (nosocomial pneumonia), inflammation, auto-PEEP, patient-ventilator asynchrony
  - cardiovascular complications
    - reduced venous return (secondary to increased intrathoracic pressure), reduced cardiac output, hypotension
  - neuromuscular complications
    - muscle atrophy
    - increased ICP
  - metabolic complications
    - decreased CO_2 due to hyperventilation
    - alkalemia with overcorrection of chronic hypercarbia

Ventilator Strategies

- mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation
- hypoxemic respiratory failure: ventilator provides supplemental O_2, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

Modes of Ventilation

- assist-control ventilation (ACV) or volume control (VC)
  - every breath is delivered with a pre-set tidal volume and rate or minute ventilation
  - extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath
- pressure control ventilation (PCV)
  - a minimum frequency is set and patient may trigger additional breaths above the ventilator
  - all breaths delivered at a pre-set constant inspiratory pressure
  - in traditional PCV, tidal volume is not guaranteed, thus changes in compliance and resistance affect tidal volume
- synchronous intermittent mandatory ventilation (SIMV)
  - ventilator provides controlled breaths (either at a set volume or pressure depending on whether in VC or PCV, respectively)
  - patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths
- pressure support ventilation (PSV)
  - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
  - useful for weaning off ventilator
- high-frequency oscillatory ventilation (HFOV)
  - high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes
  - used commonly in neonatal and pediatric respiratory failure
  - occasionally used in adults when conventional mechanical ventilation is failing
- non-invasive positive pressure ventilation (NPPV)
  - achieved without intubation by using a nasal or face mask
  - Bi-level positive airway pressure (BiPAP): increased pressure (like PSV) on inspiration and lower constant pressure on expiration (i.e. PEEP)
  - CPAP: delivers constant pressure on both inspiration and expiration

Tracheostomy
Tracheostomy should be considered in patients who require ventilator support for extended periods of time. Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities

Changes in peak pressures in ACV and tidal volumes in PCV may reflect changes in lung compliance and/or airway resistance – patient may be getting better or worse

Positive End Expiratory Pressure (PEEP)
Positive pressure applied at the end of ventilation that helps to keep alveoli open, decreasing V/Q mismatch

Used with all invasive modes of ventilation

Monitoring Ventilatory Therapy
Pulse oximetry, $ETCO_2$ concentration
Regular arterial blood gases
Assess tolerance regularly

Patients who develop a pneumothorax while on mechanical ventilation require a chest tube

Causes of Intraoperative Hypoxemia

Inadequate Oxygen Supply
e.g. breathing system disconnection, obstructed or malpositioned ETT, leaks in the anesthetic machine, loss of oxygen supply
Hypoventilation
Ventilation-Perfusion Inequalities
e.g. atelectasis, pneumonia, pulmonary edema, pneumothorax
Reduction in Oxygen Carrying Capacity
e.g. anemia, carbon monoxide poisoning, methemoglobinemia, hemoglobinopathy
Leftward Shift of the Hemoglobin-Oxygen Saturation Curve
e.g. hypothermia, decreased 2,3-BPG, alkalosis, hypocarbia, carbon monoxide poisoning
Right-to-Left Cardiac Shunt

Table 3. Causes of Abnormal End Tidal CO_2 Levels

Hypocapnea (Decreased CO_2)	Hypercapnea (Increased CO_2)
Hyperventilation	Hypoventilation
Hypothermia (decreased metabolic rate)	Malignant hyperthermia, other hypermetabolic states
Decreased pulmonary blood flow (decreased cardiac output)	Improved pulmonary blood flow after resuscitation or hypotension
Technical issues Incorrect placement of sampling catheter Inadequate sampling volume	Technical issues Water in capnography device Anesthetic breathing circuit error Inadequate fresh gas flow Rebreathing Exhausted soda lime Faulty circuit absorber valves
V/Q mismatch Pulmonary thromboembolism Incipient pulmonary edema Air embolism	Low bicarbonate

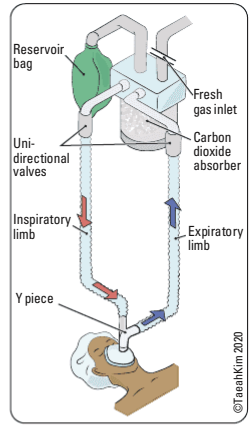


Figure 9. The anesthesia circuit

Intraoperative Management

Temperature

Causes of Hypothermia (<36.0°C)

- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
  - OR environment (e.g. cold room, IV fluids, instruments)
  - open wound
- prevent with forced air warming blankets/warm-water blankets, heated humidification of inspired gases, warmed IV fluid, and increased OR temperature

Causes of Hyperthermia (>37.5-38.3°C)

- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- hypermetabolic states (e.g. malignant hyperthermia, neuroleptic malignant syndrome, pheochromocytoma)
- over-zealous warming efforts

Impact of Hypothermia (<36°C)

Increased risk of wound infections due to impaired immune function

Increases the period of hospitalization by delaying healing

Reduces platelet function and impairs activation of coagulation cascade, increasing blood loss and transfusion requirements

Triples the incidence of VT and morbid cardiac events

Decreases the metabolism of anesthetic agents, prolonging postoperative recovery

See Landmark Anesthesiology Trials table for more information on results from study of Wound Infection and Temperature, which details the impact of normothermia on wound healing and length of stay as seen in 200 patients aged 18-80 yr who underwent elective colorectal surgery.

See Landmark Anesthesiology Trials table for more information on the PROTECT trial, which describes the effect of aggressive vs. routine warming on major cardiovascular outcomes in patients having noncardiac surgery.

Heart Rate

Cardiac Arrest

- pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-shockable rhythms
  - shockable: ventricular fibrillation (VF) and ventricular tachycardia (pVT)
  - non-shockable: asystole and pulseless electrical activity (PEA)
- for VF/pVT, key to survival is good early CPR and defibrillation
- for asystole/PEA, key to survival is good early CPR and exclusion of all reversible causes
- reversible causes of PEA arrest (5 Hs and 5 Ts)
  - 5 Hs: hypothermia, hypovolemia, hypoxia, hydrogen ions (acidosis), hypo/hyperkalemia
  - 5 Ts: tamponade (cardiac), thrombosis (pulmonary), thrombosis (coronary), tension pneumothorax, toxins (overdose/poisoning)
  - when a patient sustains a cardiac arrest during anesthesia, it is important to remember that there are other causes on top of the Hs and Ts to consider (e.g. local anesthetic systemic toxicity (LAST), excessive anesthetic dosing, etc.)
- for management of cardiac arrest, see *Appendices, A30*

Intraoperative Tachycardia

- tachycardia – HR >100 bpm; divided into sinus tachycardia (HR = 100-150 bpm) or supraventricular tachycardia (SVT)
- SVT: can be further divided into narrow complex or wide complex tachycardia
  - narrow complex: atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
  - wide complex: VT, SVT with aberrant conduction
- causes of sinus tachycardia
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis

- drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium) and withdrawal
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, pheochromocytoma, thyrotoxicosis, serotonin syndrome

• for management of tachycardia, see *Appendices, A30*

Intraoperative Bradycardia

• bradycardia – HR <50 bpm; most concerning are 2nd degree (Mobitz type II) and 3rd degree heart block, which can both degenerate into asystole
• causes of sinus bradycardia
- increased parasympathetic tone vs. decreased sympathetic tone
- must rule out hypoxemia
- arrhythmias (see Cardiology and Cardiac Surgery, C19)
- baroreceptor reflex due to increased ICP or increased BP
- vagal reflex (oculocardiac reflex, carotid sinus reflex, airway manipulation)
- drugs (e.g. opioids, edrophonium, neostigmine, halothane, digoxin, β-blockers)
- high spinal/epidural anesthesia
- hypothermia and hypothyroidism

• for management of bradycardia, see *Appendices, A30*

Blood Pressure

Causes of Intraoperative Hypotension/Shock

• shock: inability of cardiovascular system to maintain adequate end-organ perfusion and delivery of O_2 to tissues
a) septic shock
- see Infectious Diseases, ID20

b) spinal/neurogenic shock
- decreased sympathetic tone
- hypotension without tachycardia or peripheral vasoconstriction (warm skin)

c) hypovolemic/hemorrhagic shock
- most common form of shock, due to decrease in intravascular volume

d) obstructive shock
- obstruction of blood into or out of the heart
- increased JVP, distended neck veins, increased SVR, insufficient CO
- e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism (and other emboli – i.e. fat, air)

e) cardiogenic shock
- inability of the heart to pump an adequate volume of blood
- increased JVP, distended neck veins, increased SVR, decreased CO
- e.g. myocardial dysfunction, dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction

f) anaphylactic(K) shock
- see Emergency Medicine, ER3

g) endocrine/other
- transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome
- see Hematology and Endocrinology

h) drugs
- vasodilators, high spinal anesthetic interfering with sympathetic outflow

Causes of Intraoperative Hypertension

- inadequate anesthesia causing pain and anxiety
- pre-existing HTN, coarctation, or preeclampsia
- hypoxemia/hypercarbia
- hypervolemia
- increased intracranial pressure
- full bladder
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine) and withdrawal
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, pheochromocytoma (see Endocrinology, E29, E40)

Fluid Balance and Resuscitation

- total requirement = maintenance + deficit + ongoing loss
- in surgical settings, this formula must take into account multiple factors including preoperative fasting/decreased fluid intake, increased losses during or before surgery, and fluids given with blood products and medications
- increasingly, Enhanced Recovery After Surgery protocols recommend consumption of clear fluids up to 2 h prior to surgery
- both inadequate fluid resuscitation AND excessive fluid administration increase morbidity postoperatively

Intraoperative Shock Box

SHOCKED
Sepsis or Spinal shock
Hypovolemic/Hemorrhagic
Obstructive
Cardiogenic
anaphylacti**K**
Endocrine/other (e.g. Addison's disease, hyperthyroidism, transfusion reaction)
Drugs

BP = CO x SVR, where CO = SV x HR
SV is a function of preload, afterload, and contractility

Intraoperative Hypotension and the Risk of Postoperative Adverse Outcomes: A Systematic Review
Br J Anaesth 2018;4:706-721
Purpose: To determine to what extent hypotension during noncardiac surgery is associated with unfavorable outcomes.
Methods: Systematic review of RCTs, cohort studies, and case-control studies (n=42) on reported associations between intraoperative hypotension and associations with postoperative adverse outcomes after noncardiac surgery.
Results: Prolonged exposure (≥10 min) to MAPs <80 mmHg and for shorter durations <70 mmHg was associated with mildly elevated risks of end-organ injury. Increased durations for MAP <65-60 mmHg or for any exposures <55-50 mmHg were associated with moderately or highly elevated risks.
Conclusions: Organ injury may occur when MAP decreases <80 mmHg for ≥10 min. This risk increases with blood pressures becoming progressively lower.

See Landmark Anesthesiology Trials table for more information on the POISE-3 trial, which assesses the effects of a hypotension-avoidance and a hypertension-avoidance strategy on major vascular complications after noncardiac surgery.

See Landmark Anesthesiology Trials table for more information on the POISE-2 trial, which compares low-dose clonidine vs. placebo on the rate of death and major cardiovascular events in patients having noncardiac surgery.

See Landmark Anesthesiology Trials table for more information on the POISE trial, which assesses the effects of perioperative β blockers in patients having non-cardiac surgery.

Maintenance Fluid

- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (beware of renal failure)
- maintenance should not exceed 3 mL/kg/h
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation, and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres, and CHF
- maintenance electrolytes
  - Na^+: 3 mEq/kg/d
  - K^+: 1 mEq/kg/d
- 4-2-1 rule: 4 mL/h first 10 kg, 2 mL/h next 10 kg, 1 mL/h for every kg after to calculate maintenance fluid requirement
  - alternatively, may add 40 to adults who weigh ≥20kg to calculate maintenance fluid requirement in mL/h
- e.g. a 50 kg patient's maintenance requirements
  - fluid = (4 mL/h x 10 kg) + (2 mL/h x 10 kg) + (1 mL/h x 30 kg) = 40 mL/h + 20 mL/h + 30 mL/h = 90 mL/h = 2160 mL/d
  - Na^+ = 150 mEq/d (therefore 150 mEq/2.16 L/d ≈ 69 mEq/L)
  - K^+ = 50 mEq/d (therefore 50 mEq/2.16 L/d ≈ 23 mEq/L)
- above patient's requirements roughly met with 2/3 dextrose 5% in water (D5W), 1/3 normal saline (NS) 0.9%
  - 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per litre

Fluid Deficit

- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total Na^+ content determines ECF volume; [Na^+] determines ICF volume
- hypovolemia due to volume contraction
  - extra-renal Na^+ loss
    - GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - skin/respiratory: insensible losses (fever), sweating, burns
    - vascular: hemorrhage
    - renal Na^+ and H_2O loss
    - diuretics
    - osmotic diuresis
    - hypoaldosteronism
    - salt-wasting nephropathies
    - renal H_2O loss
    - diabetes insipidus (central or nephrogenic)
    - hypovolemia with normal or expanded ECF volume
    - decreased CO
    - redistribution
- hypoalbuminemia: cirrhosis, nephrotic syndrome
- capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
- replace water and electrolytes as determined by patient's needs
- with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

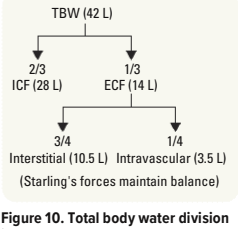


Figure 10. Total body water division in a 70 kg adult

Table 4. Signs and Symptoms of Dehydration

Percentage of Body Water Loss	Severity	Signs and Symptoms
3%	Mild	Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating
6%	Moderate	Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemoconcentration, apathy
9%	Severe	Profound oliguria or anuria and compromised CNS function with or without altered sensorium

What are the Ongoing Losses?

- traditionally thought that fluid loss during surgery resulted from blood loss, losses from Foley catheter, NG, surgical drains, and minor losses due to sequestration of fluid into other body compartments
- fluid therapy accounting for these losses often resulted in excess crystalloid administration
- goal-directed fluid regimens associated with lower rate of postoperative complications compared to predetermined calculations. These can be done using point of care ultrasound (POCUS), esophageal doppler, or pulse or pressure variation available either using arterial line monitoring or certain pulse oximetry

IV Fluids

- replacement fluids include crystalloid and colloid solutions
- IV fluids improve perfusion but NOT O_2 carrying capacity of blood

Initial Distribution of IV Fluids

- H_2O follows ions/molecules to their respective compartments

Crystalloid Infusion

- salt-containing solutions that distribute only within ECF
- consensus guidelines recommend use of balanced crystalloid (i.e. Ringer's lactate) over NS for routine replacement and resuscitation
- maintain euvolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement)
- best practice is to use goal-directed therapy
- if large volumes are to be given, use balanced fluids such as Ringer's lactate or Plasmalyte®, as too much NS may lead to hyperchloremic metabolic acidosis

Colloid Infusion

- includes protein colloids (albumin and gelatin solutions) and non-protein colloids (dextrans and starches, (e.g. hydroxyethyl starch) (HES))
- distributes within intravascular volume
- 1:1 ratio (infusion:blood loss) only in terms of replacing intravascular volume
- the use of HES solutions is controversial because of recent RCTs and meta-analyses highlighting their renal (especially in septic patients) and coagulopathic side effects, as well as a lack of specific indications for their use
  - colloids are being used based on mechanistic and experimental evidence but there is a paucity of definitive studies investigating their safety and efficacy; routine use of colloids should be avoided

Table 5. IV Fluid Solutions

		ECF	Ringer's Lactate	0.9% NS	0.45% NS in D5W	D5W	2/3 D5W + 1/3 NS	Plasmalyte
mEq/L	Na^+	142	130	154	77	-	51	140
	K^+	4	4	-	-	-	-	5
	Ca^{2+}	4	3	-	-	-	-	-
	Mg^{2+}	3	-	-	-	-	-	3
	Cl^-	103	109	154	77	-	51	98
	HCO_3^-	27	28*	-	-	-	-	27
mOsm/L		280-310	273	308	154	252	269	294
pH		7.4	6.5	5.0	4.5	4.0	4.3	7.4

*Converted from lactate

Table 6. Colloid HES Solutions

	Concentration	Plasma Volume Expansion	Duration (h)	Maximum Daily Dose (mL/kg)
Voluven®	6%	1:1	4-6	33-50
Pentaspan®	10%	1:1.2-1.5	18-24	28

Blood Products

- see Hematology, H54

Colloids vs. Crystalloids for Fluid Resuscitation in Critically Ill People
Cochrane DB Syst Rev 2018:CD000567
Purpose: To assess effect of colloids vs. crystalloids in critically ill patients on mortality, need for transfusions or renal replacement therapy, and adverse events.
Methods: Systematic review of RCTs and quasi-RCTs involving trauma, burns, or medical conditions (i.e. sepsis). Searched CENTRAL, MEDLINE, and Embase.
Outcomes: 69 studies, 30020 participants. Starches, dextrans, albumin or FFP (moderate-certainty evidence), or gelatins (low-certainty evidence) vs. crystalloids has no difference on mortality. Starches slightly increase the need for blood transfusion (moderate-certainty evidence), and albumin or FFP may make little or no difference to the need for renal replacement therapy (low-certainty evidence). Evidence for blood transfusions for dextrans, and albumin or FFP, is uncertain.

Calculating Acceptable Blood Losses (ABL)

- Blood volume
  term infant 80 mL/kg
  adult male 70 mL/kg
  adult female 60 mL/kg
- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
  EBV = 70 kg x 70 mL/kg = 4900 mL
- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion (e.g. 70 g/L for a person with Hb(initial) = 150 g/L)
  Hb(final) = 70 g/L
- Calculate

$$\text{ABL} = \text{Hb(i)} - \frac{\text{Hb(f)} \times \text{EBV}}{\text{Hb(i)}} = 150 - \frac{70 \times 4900}{150} = 2613 \text{ mL}$$

Therefore, in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost

Transfusion Infection Risks

Virus	Risk per 1 unit pRBCs
HIV	1 in 21 million
Hepatitis C virus	1 in 13 million
Hepatitis B virus	1 in 7.5 million
HTLV	1 in 1-1.3 million
Symptomatic Bacterial Sepsis	1 in 40,000 from platelets and 1 in 250,000 from RBC
West Nile virus	No cases since 2003

Source: Callum JL, Pinkerton PH. Bloody Easy. Fourth Edition ed. Toronto: Sunnybrook and Women's College Health Science Centre; 2016

See Landmark Anesthesiology Trials table for more information on the RELIEF trial, which compares the risk of complications for restrictive vs. liberal IV fluid regimen in patients having major abdominal surgery.

Induction

Routine Induction vs. Rapid Sequence Induction

- routine induction is the standard in general anesthesia; however, an RSI is indicated in patients at risk of regurgitation/aspiration (see *Aspiration, A6*)
- RSI uses
  1. pre-determined doses of induction drugs given in rapid succession to minimize the time patient is at risk for aspiration (e.g. from the time when they are unconscious without an ETT until the time when the ETT is inserted and the cuff inflated)
  2. no bag mask ventilation
  3. cricoid pressure may be applied (although there are some exceptions, e.g. trauma to upper airway)
  4. use of rapid onset muscle relaxant (i.e. SCh)

Table 7. Comparison of Routine Induction vs. RSI

Steps	Routine Induction	RSI
Equipment Preparation	Check equipment, drugs, suction, and monitors; prepare an alternative laryngoscope blade and a second ETT one size smaller, suction on	
Pre-Oxygenation/ Denitrogenation	100% O_2 for 3 min or 4-8 vital capacity breaths; reduce risk of hypoxemia during apneic period following induction	
Pre-Treatment Agents	Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy	Use agent of choice to blunt physiologic responses to airway manipulation; if possible, give 3 min prior to laryngoscopy, but can skip this step in an emergent situation
Induction Agents	Use IV or inhalation induction agent of choice	Use pre-determined dose of fast acting induction agent of choice
Muscle Relaxants	Muscle relaxant of choice given after the onset of the induction agent	Pre-determined dose of fast acting muscle relaxant (SCh or high dose rocuronium) given IMMEDIATELY after induction agent
Ventilation	Bag-mask ventilation	DO NOT bag ventilate – can increase risk of aspiration
Additional Helpful Maneuvers	External Laryngeal Manipulation using Backwards, Upwards, Rightward Pressure (BURP)	Cricoid pressure (Sellick Maneuver) to prevent regurgitation
Intubation	Intubate, inflate cuff, confirm ETT position	Intubate once paralyzed (≈45 s after SCh given), inflate cuff, confirm ETT position; cricoid pressure maintained until ETT cuff inflated and placement confirmed
Secure	Secure ETT, and begin manual/machine ventilation	

Induction Agents

- induction of general anesthesia may be achieved with intravenous agents and/or volatile inhalational agents

Intravenous Agents

- IV induction agents are non-opioid drugs used to provide hypnosis, amnesia, and blunt reflexes to laryngoscopy
- these are initially used to establish the plane of anesthesia rapidly and smoothly
  - most commonly used is propofol or ketamine
  - a continuous propofol infusion may be used as an alternative to inhalational volatile agents during the maintenance phase of general anesthesia. An indication would be malignant hyperthermia

Table 8. Intravenous Induction Agents

	Propofol (Diprivan®)	Thiopental (sodium thiopental, sodium thiopentone)*	Ketamine (Ketalar®, Ketaject®)	Etomidate	Methohexital (Brevital®)
Class	Alkylphenol – hypnotic	Short acting thiobarbiturate – hypnotic	Phencyclidine (PCP) derivative – dissociative	Imidazole derivative - hypnotic	Ultra short-acting barbiturate
Action	Inhibitory at GABA synapse Decreased cerebral metabolic rate and blood flow, decreased ICP, decreased SVR, decreased BP, and decreased SV	Inhibitory at GABA synapse Decreased cerebral metabolic rate and blood flow, decreased CPP, decreased CO, decreased BP, decreased reflex tachycardia, decreased respiration	May act on NMDA (antagonistically), opiate, and other receptors Increased HR, increased BP, increased SVR, increased coronary flow, increased myocardial O^2 uptake CNS and respiratory depression, bronchial smooth muscle relaxation	Decreases concentration of GABA required to activate receptor CNS depression Minimal cardiac or respiratory depression	Binds to the chloride ionophore site of GABA-A receptor
Indications	Induction Maintenance Total intravenous anesthesia (TIVA)	Induction Control of convulsive states, obstetric patients	Induction when sympathetic stimulation required (e.g. major trauma, hypovolemia), IM induction in children/uncooperative adults (i.e. when there is lack of IV access), severe asthma because sympathomimetic	Induction Poor cardiac function, severe valve lesions, uncontrolled hypertension	Procedural induction Electroconvulsive therapy (ECT)

*As of 2011, Thiopental has been discontinued from production for North America

Rocuronium vs. Succinylcholine for Rapid Sequence Induction Intubation
Cochrane DB Syst Rev 2015:CD002788
Purpose: Whether rocuronium creates intubating conditions comparable to those of succinylcholine during RSI intubations.
Methods: Systematic review of RCTs or CCTs with a dose of at least 0.6 mg/kg for rocuronium and 1 mg/kg for succinylcholine.
Results: 50 trials, 4151 participants. Succinylcholine was superior to rocuronium for achieving excellent intubating conditions (RR 0.86, 95% CI 0.81-0.92) and clinically acceptable intubation conditions (RR 0.97, 95% CI 0.95-0.99).
Conclusion: Succinylcholine created superior intubation conditions to rocuronium in achieving excellent and clinically acceptable intubating conditions.

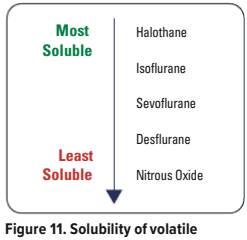


Figure 11. Solubility of volatile anesthetics in blood

Effects of Cricoid Pressure Compared with a Sham Procedure in the Rapid Sequence Induction of Anesthesia: The Iris Randomized Clinical Trial
JAMA Surg 2019;154(1):9–17
Purpose: To determine if cricoid pressure impacts pulmonary aspiration in people undergoing rapid sequence induction (RSI) of anesthesia.
Methods: Randomized and double-blind trial to assess 3472 patients undergoing rapid sequence induction of anesthesia at 10 academic centers.
Results: Results demonstrated that patients undergoing anesthesia using RSI experience increased prevention of pulmonary aspiration using cricoid pressure when compared to the sham condition.
Conclusion: This study provides evidence to show the benefit of cricoid pressure in RSI and found that it is superior to the sham procedure in preventing aspiration.

Table 8. Intravenous Induction Agents

	Propofol (Diprivan®)	Thiopental (sodium thiopental, sodium thiopentone)*	Ketamine (Ketalar®, Ketaject®)	Etomidate	Methohexital (Brevital®)
Caution	Patients who cannot tolerate sudden decreased BP (e.g. fixed cardiac output or shock)	Allergy to barbiturates Uncontrolled hypotension, shock, cardiac failure Porphyria, liver disease, status asthmaticus, myxedema	Ketamine allergy TCA medication (interaction causes HTN and dysrhythmias) History of psychosis Patients who cannot tolerate HTN (e.g. CHF, increased ICP, aneurysm)	Postoperative nausea and vomiting Venous irritation	Contraindicated in acute intermittent porphyria
Dosing	IV induction: 1.5-2.5 mg/kg (less with opioids) Unconscious <1 min Lasts 4-6 min $t_{1/2}$ = 55 min Decreased postoperative sedation, recovery time, N/V	IV induction: 3-5 mg/kg Unconscious about 30 s Lasts 5 min Accumulation with repeat dosing – not for maintenance $t_{1/2}$ = 5-10 h Postoperative sedation lasts hours	IV induction 1-2 mg/kg Dissociation in 15 s, analgesia, amnesia, and unconsciousness in 45-60 s Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 h $t_{1/2}$ = ~3 h	IV induction 0. 3 mg/kg Onset 30-60 s Lasts 4-8 min	IV induction 1 to 1.5 mg/kg of a 1% solution; doses must be titrated to effect
Special Considerations	-30% decreased BP due to vasodilation Reduce burning at IV site by mixing with lidocaine	Combining with rocuronium causes precipitates to form	High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions) Pretreat with glycopyrrolate to decrease salivation	Adrenal suppression after first dose, cannot repeat dose or use as infusion Myoclonic movements during induction	

*As of 2011, Thiopental has been discontinued from production for North America

Volatile Inhalational Agents

- e.g. sevoflurane, desflurane, isoflurane, enflurane, halothane, and nitrous oxide

Table 9. Volatile Inhalational Agents

	Sevoflurane	Desflurane*	Isoflurane**	Enflurane	Halothane	Nitrous oxide (N_2O)***
MAC (% gas in O_2)	2.0	6.0	1.2	1.7	0.8	104
CNS	Increased ICP	Increased ICP	Decreased cerebral metabolic rate Increased ICP	ECG seizure-like activity Increased ICP	Increased ICP and cerebral blood flow	—
Resp	Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory CO_2 reflexes, bronchodilation					—
CVS	Less decrease of contractility, stable HR	Tachycardia with rapid increase in concentration	Decreased BP and CO, increased HR, theoretical chance of coronary steal**	Stable HR, decreased contractility	Decreased BP, CO, HR, and conduction Sensitizes myocardium to epinephrine-induced arrhythmias	Can cause decreased HR in pediatric patients with existing heart disease
MSK	Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation					

*Airway irritant: desflurane can provoke breath holding, laryngospasm, and salivation, so it is not used for inhalational induction
**Coronary steal: isoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion (e.g. stents, atherosclerosis)
***Properties and Adverse Effects of N_2O
Due to its high MAC, N_2O is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only
Second Gas Effect
Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen, and ETT cuff will markedly enlarge if N_2O is administered
Diffusion hypoxia: during anesthesia, the washout of N_2O from body stores into alveoli can dilute the alveolar [O_2], creating a hypoxic mixture if the original [O_2] is low

See Landmark Anesthesiology Trials table for more information on MYRIAD trial, which details the impact of volatile anesthetics vs. total intravenous anesthesia in patients undergoing CABG.

Minimum Alveolar Concentration

- minimum alveolar concentration (MAC) is the minimal alveolar concentration of a volatile anesthetic required (at one atmosphere of pressure in 100% oxygen) that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- potency of inhalational agents is compared using MAC
- MAC of halogenated volatile anesthetics decreases by approximately 6% per additional decade of age in adults
- 1.2-1.3 times MAC will often ablate response to stimuli in the general population
- MAC values are roughly additive when mixing N_2O with another volatile agent; however, this only applies to movement, not other effects such as BP changes (e.g. 0.5 MAC of a potent agent + 0.5 MAC of N_2O = 1 MAC of potent agent)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation; generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli; generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command; generally 0.3-0.4 of the usual MAC

Factors increasing MAC: chronic alcohol use, hyperthyroidism, hyperthermia, acute amphetamine use, cannabinoids, young age
Factors decreasing MAC: acute alcohol intoxication, hypothermia, sedating drugs, advanced age, chronic amphetamine use, drugs (opioids, benzodiazepines), α 2 adrenergic agonists, nitrous oxide, IV anesthetics, shock

See Landmark Anesthesiology Trials table for more information on the ENIGMA-II trial, which evaluates the rate of cardiovascular complications in patients receiving nitrous oxide (NO) or NO-free anesthesia.

Muscle Relaxants and Reversing Agents

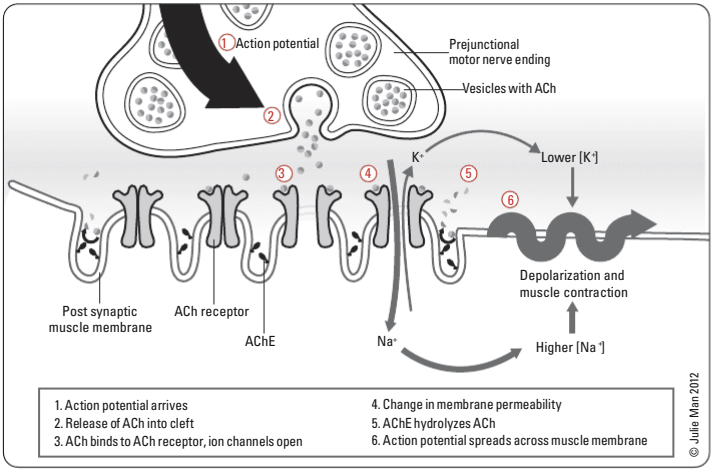


Figure 12. Review of anatomy and physiology of the neuromuscular junction (NMJ)

Muscle Relaxants

- two types of muscle relaxants
    1. depolarizing muscle relaxants: SCh
    2. non-depolarizing muscle relaxants (NDMRs): rocuronium, mivacurium, vecuronium, cisatracurium, pancuronium
- block nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- never use muscle relaxants without adequate preparation and equipment to maintain airway and ventilation
- muscle relaxation produces the following desired effects:
    1. facilitates intubation
    2. assists with mechanical ventilation
    3. prevents muscle stretch reflex and decreases muscle tone
    4. allows access to the surgical field (intracavity surgery)
- nerve stimulator (i.e. train of four) is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade

Pseudocholinesterase
Pseudocholinesterase is produced by the liver and metabolizes SCh and mivacurium. A prolonged duration of blockade by SCh occurs with:
(a) decreased quantity of plasma cholinesterase (e.g. congenital (hereditary), liver disease, pregnancy, malignancy, malnutrition, collagen vascular disease, hypothyroidism)
(b) abnormal quality of plasma cholinesterase (e.g. normal levels but impaired activity of enzymes, genetically inherited)

Table 10. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)

Mechanism of Action	Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh
Intubating Dose (mg/kg)	1-1.5
Onset	30-60 s – rapid (fastest of all muscle relaxants)
Duration	3-5 min – short (no reversing agent for SCh)
Metabolism	SCh is hydrolyzed by plasma cholinesterase (i.e. pseudocholinesterase), found only in plasma and not at the NMJ
Indications	Assist intubation Increased risk of aspiration (e.g. full stomach, hiatus hernia, obesity, pregnancy, trauma); need rapid paralysis and airway control Short procedures Electroconvulsive Therapy (ECT) Laryngospasm
Side Effects	1. Simulation of muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors) may cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children) 2. Hyperkalemia Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells Patients at risk: 3rd degree burns 24 h-6 mo after injury Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy) Severe intra-abdominal infections Severe closed head injury Upper motor neuron lesions 3. Can trigger MH (see *Malignant Hyperthermia, A29*) 4. Increased ICP/intraocular pressure/intragastric pressure (no increased risk of aspiration if competent LES) 5. Fasciculations, postoperative myalgia – may be minimized if small dose of NMBA given before SCh administration
Contraindications	
Absolute	Known hypersensitivity or allergy, positive history of MH, myotonia (m. congenita, m. dystrophica, paramyotonia congenital), high-risk for hyperkalemic response
Relative	Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury

Table 11. Non-Depolarizing Muscle Relaxants (Competitive)

Mechanism of Action	Competitive blockade of postsynaptic ACh receptors preventing depolarization				
Classification	**Short**		**Intermediate**		**Long**
	Mivacurium	Rocuronium	Vecuronium	Cisatracurium	Pancuronium
Intubating Dose (mg/kg)	0.2	0.6-1.0	0.1	0.2	0.1
Onset (min)	2-3	1.5	2-3	3	3-5
Duration (min)	15-25	30-45	45-60	40-60	90-120
Metabolism	Plasma cholinesterase	Liver (major) Renal (minor)	Liver	Hofmann Elimination	Renal (major) Liver (minor)
Intubating Dose (mg/kg)	0.2	0.6-1.0	0.1	0.2	0.1
Indications	Assist intubation, assist mechanical ventilation in some ICU patients, and reduce fasciculations and postoperative myalgias secondary to SCh				
Side Effects					
Histamine Release	Yes	No	No	No	No
Other	—	—	—	—	Tachycardia
Considerations	Increased duration of action in renal or liver failure	Quick onset of rocuronium allows its use in rapid sequence induction	—	Good for patients with renal or hepatic insufficiency	Use when increased HR and BP desired

Reversal Agents

- sugammadex is a selective relaxant binding agent and can be administered immediately after dose of NDMR
- neostigmine, pyridostigmine, and edrophonium are acetylcholinesterase inhibitors - these are competitive inhibitors and therefore can only be administered when there has been some recovery of blockade (i.e. train of four muscle response to stimulation)
- can only reverse the effects of NDMRs
- anticholinergic agents (e.g. atropine, glycopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation, increased peristalsis, and bronchoconstriction)

Table 12. Reversal Agents for Non-Depolarizing Relaxants

Agent	Pyridostigmine	Neostigmine	Edrophonium	Sugammadex
Onset	Slow	Intermediate	Intermediate	Fast
Mechanism of Action	AChE; inhibit enzymatic degradation of ACh, increase ACh at nicotinic and muscarinic receptors, displace NDMRs Muscarinic effects of reversing agents include unwanted bradycardia, salivation, and increased bowel peristalsis*			Encapsulates and inactivates rocuronium and vecuronium → ↓ amount of agent available to bind to receptors in NMJ
Dose (mg/kg)	0.1-0.4	0.04-0.08	0.5-1	2-16
Recommended Anticholinergic	Glycopyrrolate	Glycopyrrolate	Atropine	N/A
Dose of Anticholinergic (per mg)	0.05 mg	0.2 mg	0.014 mg	N/A

*Atropine and glycopyrrolate are anticholinergic agents administered to minimize muscarinic effects of reversal agents

Analgesia

- opioids are used during induction to provide analgesia, sedation, and blunt autonomic responses
- their sedative properties supplement the IV induction agent and they blunt autonomic response during laryngoscopy and intubation

Maintenance

- general anesthesia is maintained using volatile inhalation agents and/or IV agents (i.e. propofol infusion)
- analgesia (usually IV opioids)
  - ± muscle relaxants given as needed

See Landmark Anesthesiology Trials table for more information on results from the ENGAGES trial, which details the efficacy of using EEG guided anesthetic administration in patients with postoperative delirium.

Extubation

- criteria: patient must no longer have intubation requirements
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- general guidelines
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - allow ventilation (spontaneous or controlled) with 100% O_2 for 3-5 min
  - suction secretions from pharynx, deflate cuff, remove ETT on inspiration (vocal cords abducted)
  - ensure patient is breathing adequately after extubation
  - ensure face mask for O_2 delivery available
  - proper positioning of patient during transfer to recovery room (supine, head elevated)

Complications of Extubation

- early extubation: aspiration, laryngospasm
- late extubation: transient vocal cord incompetence, edema (glottic, subglottic), pharyngitis, tracheitis

Laryngospasm

- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (by oropharyngeal secretions, blood, early extubation)
- causes partial or total airway obstruction
- more likely to occur in semi-conscious patients
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: suction, remove oral airway/LMA, apply CPAP with anesthetic reservoir bag and partial closure of adjustable pressure-limiting (APL) valve, BMV with 100% O_2, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose SCh (approximately 0.25 mg/kg), and re-intubate if hypoxia develops

Regional Anesthesia

- local anesthetic applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) to reduce or prevent impulse transmission
- no CNS depression (unless overdose of LA); patient remains conscious
- regional anesthetic techniques categorized as follows:
  - epidural and spinal anesthesia (neuraxial anesthesia)
  - peripheral nerve blocks
  - IV regional anesthesia (e.g. Bier block)

Patient Preparation
- sedation and/or anxiolysis may be indicated before block
- monitoring should be as extensive as for GA

Epidural and Spinal Anesthesia

- most common for surgeries performed below the level of umbilicus but can be extended to any level (useful in thoracic, abdominal, and lower extremity surgeries)
- typically placed in thoracic or lumbar spine

Anatomy of Spinal/Epidural Area
- spinal cord extends to L1; dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated (superficial to deep)
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

Table 13. Epidural vs. Spinal Anesthesia

	Epidural	Spinal
Deposition Site	LA injected in epidural space (space between ligamentum flavum and dura) Initial blockade is at the spinal roots followed by some degree of spinal cord anesthesia as LA diffuses into the subarachnoid space through the dura	LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots
Onset	Significant blockade requires 10-15 min Slower onset of side effects	Rapid blockade (onset in 2-5 min)
Effectiveness	Effectiveness of blockade can be variable	Very effective blockade
Difficulty	Technically more difficult; greater failure rate	Easier to perform due to visual confirmation of CSF flow
Patient Positioning Post-injection	Position of patient not as important; specific gravity not an issue	Hyperbaric LA solution – position of patient important
Specific Gravity/ Spread	Epidural injections spread throughout the potential space; specific gravity of solution does not affect spread	LA solution may be made hyperbaric (of greater specific gravity than the CSF by mixing with dextrose 10%, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space)
Dosage	Larger volume/dose of LA (usually > toxic IV dose)	Smaller dose of LA required (usually < toxic IV dose)
Continuous Infusion	Use of catheter allows for continuous infusion or repeat injections	None
Complications	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T4 block), e.g. "high block" Epidural or subarachnoid hematoma Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications) Systemic toxicity of LA (accidental intravenous) Catheter complications (shearing, kinking, vascular, or subarachnoid placement) Infection Post-dural puncture	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T4 block), e.g. "high spinal" Epidural or subarachnoid hematoma Post-spinal headache (CSF leak) Transient paresthesias Spinal cord trauma Infection
Combined Spinal-Epidural	Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter	

Benefits of Regional Anesthesia
- Reduced perioperative pulmonary complications
- Reduced perioperative analgesia requirements
- Decreased PONV
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE
- Shorter recovery and improved rehabilitation
- Pain blockade with preserved motor function

Landmarking Epidural/Spinal Anesthesia
- Spinous processes should be maximally flexed
- L4 spinous processes found between iliac crests
- T7 landmark at the tip of the scapula

Classic Presentation of Dural Puncture Headache
- Onset 6 h-3 d after dural puncture
- Postural component (worse when sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia

Effect of Anaesthesia Type on Postoperative Mortality and Morbidities: A Matched Analysis of the NSQIP Database
Br J Anaesth 2017;118:105-111
Purpose: Determine the effects of RA vs. GA on postoperative survival and morbidities.
Methods: Matched surgical procedures and type of anesthesia using the US National Surgical Quality Improvement database. Primary outcome was 30 d postoperative mortality and secondary outcomes were hospital length of stay and postoperative organ system dysfunction.
Results: There was no difference in 30 d mortality. RA was significantly associated with increased likelihood of early discharge (HR 1.09; P< 0.001). There were lower odds of intraoperative complications (47%), respiratory complications (24%), DVT (16%), and any one postoperative complication (15%) (OR 0.85; P < 0.001).
Conclusion: RA was associated with significantly lower odds of several postoperative complications, decreased hospital length of stay, but not mortality when compared with GA.

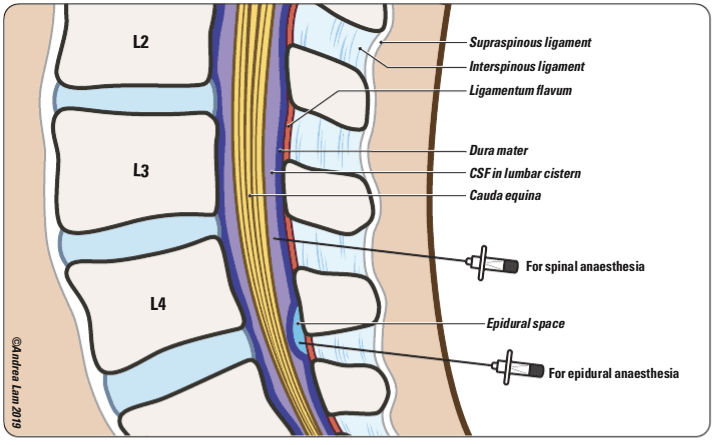


Figure 14. Sagittal cross-section of the anatomy of neuraxial anesthesia

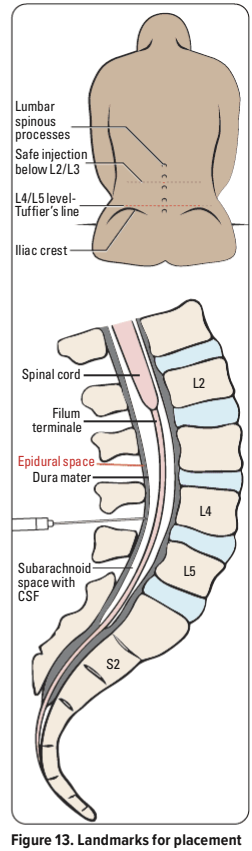


Figure 13. Landmarks for placement of epidural/spinal anesthesia

Contraindications to Spinal/Epidural Anesthesia

- absolute contraindications
  - lack of resuscitative drugs/equipment
  - patient refusal
  - allergy to local anesthetic
  - infection at puncture site or underlying tissues
  - coagulopathies/bleeding diathesis
  - raised ICP
  - sepsis/bacteremia
  - severe hypovolemia
  - cardiac lesion with fixed output states (e.g. severe mitral/aortic stenosis)
  - lack of IV access
- relative contraindications
  - pre-existing neurological disease (e.g. demyelinating lesions)
  - previous spinal surgery; severe spinal deformity
  - prolonged surgery
  - major blood loss or maneuvers that can compromise reaction

Peripheral Nerve Blocks

- deposition of LA around the target nerve or plexus
- ultrasound guidance and peripheral nerve stimulation may be used to guide needle to target/stimulate nerve while avoiding neural trauma or intraneural injection
- most major nerves or nerve plexuses can be targeted (e.g. brachial plexus block, femoral nerve block, sciatic nerve block)
- performed with standard monitors
- risk of late neurologic injury is approximately 2-4/10000 peripheral nerve blocks
- resuscitation equipment must be available

Contraindications to Peripheral Nerve Blockade

- absolute contraindications
  - allergy to LA
  - patient refusal
- relative contraindications
  - certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
  - local infection at block site
  - bleeding disorder

Local Anesthesia

Local Anesthetic Agents

- see *Table 14, A23, for list of LA agents*

Definition and Mode of Action
- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptors on the cytosolic side of the Na^+ channels, inhibiting Na^+ flux and thus blocking impulse conduction
- different types of nerve fibres undergo blockade at different rates

Absorption, Distribution, and Metabolism
- LA readily crosses the BBB once absorbed into the bloodstream
- ester-type LA (e.g. procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- amide-type LA (e.g. lidocaine, bupivacaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

Selection of LA
- choice of LA depends on:
  - onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA, and the faster the onset of action)
  - duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  - potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  - unique needs (e.g. sensory blockade with relative preservation of motor function by bupivacaine at low doses)
  - potential for toxicity

Table 14. Local Anesthetic Agents

	Maximum Dose (mg/kg)	Maximum Dose with Epinephrine (mg/kg)	Potency	Duration	Onset
Chloroprocaine	11	14	Low	15-30 min	Fast
Lidocaine	5	7	Medium	1-2 h	Fast
Mepivacaine	5	7	Medium	3-6 h	Fast
Bupivacaine	2.5	3	High	3-8 h	Slow
Ropivacaine	2.5	3	High	2-8 h	Medium

Systemic Toxicity
- see *Table 14* for maximum doses, potency, and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption

CNS Effects
- first appear to be excitatory due to initial block of inhibitory fibres, followed by subsequent blockade of excitatory fibres
- effects in order of appearance
  - numbness of tongue, perioral tingling, metallic taste
  - disorientation, drowsiness
  - tinnitus
  - visual disturbances
  - muscle twitching, tremors
  - unconsciousness
  - convulsions, seizures
  - generalized CNS depression, coma, respiratory arrest

CVS Effects
- vasodilation, hypotension
- decreased myocardial contractility
- dose-dependent delay in cardiac impulse transmission
  - prolonged PR, QRS intervals
  - sinus bradycardia
- CVS collapse

Treatment of Systemic Toxicity
- early recognition of signs; get help
- 100% O_2, manage ABCs
- diazepam or other anticonvulsant to prevent potential onset of seizures
- manage arrhythmias
- Intralipid® 20% to bind local anesthetic in circulation

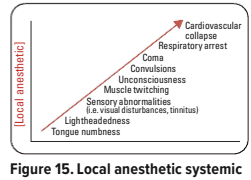


Figure 15. Local anesthetic systemic toxicity

Local Infiltration and Hematoma Blocks

Local Infiltration
- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerves
- suitable for small incisions, suturing, and excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100000-1:200000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

Fracture Hematoma Block
- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

Topical Anesthetics

- various preparations of LAs available for topical use, which may be a mixture of agents (e.g. EMLA® cream is a combination of lidocaine 2.5% and prilocaine)
- must be able to penetrate the skin or mucous membrane

Postoperative Care

- pain management should be continuous from OR to PACU to hospital ward and home

Common Postoperative Anesthetic Complications

Uncontrolled/Poorly Controlled Pain
- See below

Nausea and Vomiting
- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), ondansetron (Zofran®), granisetron (Kytril®), dexamethasone (Decadron®), metoclopramide (Maxeran®; not with bowel obstruction), prochlorperazine (Stemetil®)

Confusion and Agitation
- ABCs first – confusion or agitation can be caused by airway obstruction, hypercapnia, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers, language barriers
- metabolic disturbance (e.g. hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (e.g. stroke, raised ICP)
- drug effect (e.g. ketamine, anticholinergics, serotonin, benzodiazepines, opioids)
- elderly patients are more susceptible to postoperative delirium

Respiratory Complications
- susceptible to aspiration of gastric contents due to PONV and unreliable airway reflexes
- airway obstruction (secondary to reduced muscle tone from residual anesthetic, soft tissue trauma and edema, or pooled secretions) may lead to inadequate ventilation, hypoxemia, and hypercapnia
- airway obstruction can often be relieved with head tilt, jaw elevation, and anterior displacement of the mandible. If the obstruction is not reversible, a nasal or oral airway may be used

Hypotension
- must be identified and treated quickly to prevent inadequate perfusion and ischemic damage
- reduced cardiac output (the most common cause is hypovolemia) and/or peripheral vasodilation (e.g. residual anesthetic agent)
- first step in treatment is usually the administration of fluids ± inotropic agents

Hypertension
- pain, hypercapnia, hypoxemia, increased intravascular fluid volume, and sympathomimetic drugs can cause hypertension
- IV nitroglycerin, hydralazine, calcium channel blockers, or β-blocking drugs (e.g. esmolol and metoprolol) can be used to treat hypertension

Local Anesthetics and Regional Anaesthesia vs. Conventional Analgesia for Preventing Persistent Postoperative Pain in Adults and Children
Cochrane DB Syst Rev 2018;6:CD007105
Purpose: Compare LA and RA vs. conventional anesthesia for the prevention of persistent postoperative pain (PPP) beyond 3 mo.
Methods: Searched CENTRAL, MEDLINE, and Embase to December 2016. RCTs comparing RA vs. conventional anesthesia were included.
Results: Total 63 RCTs included. Data on RA for the prevention of PPP beyond 3 mo after surgery from 39 studies, enrolling a total of 3027 participants in inclusive analysis. Moderate quality evidence favoring RA over conventional for thoracotomy, C-section (OR 0.52 and OR 0.46 respectively). Moderate quality evidence showing the infusion of IV LA for the prevention of PPP 3-6 mo after breast cancer surgery with an OR of 0.24. Low quality evidence in RA for the prevention of PPP 3-12 mo after breast cancer surgery with an OR of 0.43.
Conclusions: There is moderate-quality evidence that RA may reduce the risk of developing PPP after 3-18 mo after thoracotomy and 3-12 mo after cesarean section. Further studies including larger populations are needed.

Risk Factors for PONV
- Young age*
- Female*
- History of PONV*
- Non-smoker*
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: N_2O, opioids, volatile agents

*These factors refer to the Apfel tool for PONV risk stratification and management

See Landmark Anesthesiology Trials table for more information on results from the IMPACT trial which compares the efficacy of six well-established prophylactic antiemetic interventions in patients scheduled to undergo elective surgery during general anesthesia at high risk for postoperative nausea and vomiting.

See Landmark Anesthesiology Trials table for more information on results from the DREAMS trial, which details the effect of preoperative dexamethasone administration in patients with postoperative vomiting.

See Landmark Anesthesiology Trials table for more information on the BALANCEDLT trial, which compares all-cause-1 yr mortality in light vs. deep GA in patients having major surgery.

Pain Management

Definitions

- pain: an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (International Association for the Study of Pain (IASP); definition updated in 2020)
- nociception: detection, transduction, and transmission of noxious stimuli

Pain Classifications

- temporal: acute vs. chronic
- mechanism: nociceptive vs. neuropathic

Acute Pain

- pain of short duration (<6 wk) usually associated with surgery, trauma, or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

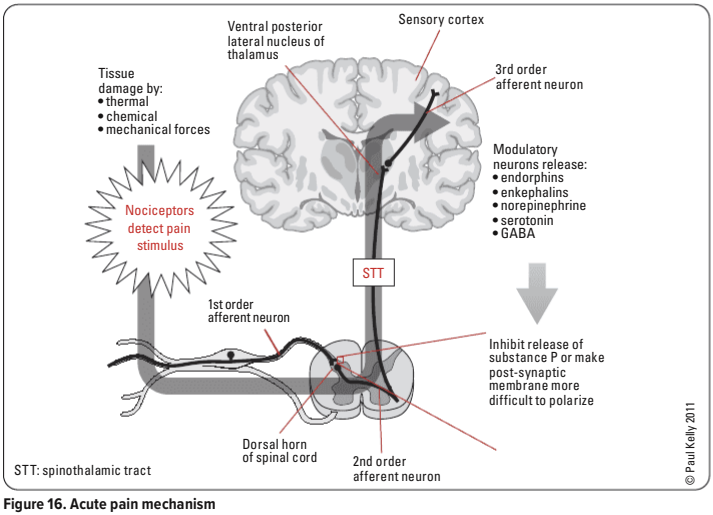


Figure 16. Acute pain mechanism

Pharmacological Management of Acute Pain

- ask the patient to rate the pain out of 10 or use visual analog scale to determine severity
- pharmacological treatment guided by WHO analgesia ladder (*Figure 17*)

Table 15. Commonly Used Analgesics

	Acetaminophen	NSAIDs	Opioids
Examples	Tylenol®	Aspirin®, ibuprofen, naproxen, ketorolac (IV)	Oral: codeine, oxycodone, morphine, hydromorphone Parenteral: morphine, hydromorphone, fentanyl
Indications	First-line for mild acute pain	Mild-moderate pain	Oral: moderate acute pain Parenteral: moderate-severe acute pain
Mechanism of Action	Unclear, hypothesized cyclooxygenase-2 (COX-2) inhibition Unclear, hypothesized modulation of endogenous cannabinoid system	Non-selective COX-1 and -2 inhibition reducing proinflammatory prostaglandin synthesis	Dampens nociceptive transmission between 1st and 2nd order neurons in the dorsal horn Activates ascending modulatory pathways resulting in release of inhibitory neurotransmitters Inhibits peripheral inflammatory response and hyperalgesia Affects mood and anxiety – alleviates the affective component of perceived pain
Dosing/ Administration	Limited by analgesic ceiling beyond which there is no additional analgesia Opioid-sparing Max dose of 4 g/24 h	Limited by analgesic ceiling beyond which there is no additional analgesia Opioid-sparing Significant inter-individual variation in efficacy	No analgesic ceiling (except for codeine) Can be administered intrathecally (e.g. spinal block) or by continuous infusion Consider breakthrough dose and/or co-administration with anti-emetics, laxatives

Comparison of Intraoperative Sedation with Dexmedetomidine vs. Propofol on Acute Postoperative Pain in Total Knee Arthroplasty under Spinal Anesthesia: A Randomized Trial
Anesth Analg 2019;129:1512-1518
Purpose: Compare the postoperative analgesic effect of intraoperative sedation with dexmedetomidine (DEX) vs. propofol.
Methods: Patients (n=48) were randomly assigned to DEX or propofol. After the initial pre-determined loading dose, drug infusion rate was determined according to sedation level. Cumulative amounts of PCA fentanyl were recorded at 24-48 h postoperatively (primary outcome). The postoperative numerical rating scale for pain was assessed at 6, 12, 24, and 48 h (secondary outcome).
Results: DEX significantly reduced postoperative fentanyl consumption at all of the studies' time points. The numerical rating scale for pain was significantly lower at all time points.
Conclusion: Intraoperative DEX sedation was associated with a small but clinically important reduction in postoperative opioid use after total knee arthroplasty.

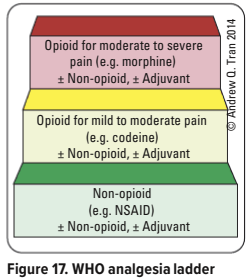

Opioid for moderate to severe pain (e.g. morphine)
± Non-opioid, ± Adjuvant
Opioid for mild to moderate pain (e.g. codeine)
± Non-opioid, ± Adjuvant
Non-opioid (e.g. NSAID)
± Non-opioid, ± Adjuvant
© Andrew D. Tran 2014

Figure 17. WHO analgesia ladder

Cautionary Use of NSAIDs in Patients with:
Asthma
Coagulopathy
GI ulcers
Renal insufficiency
Pregnancy, 3rd trimester

Table 15. Commonly Used Analgesics

	Acetaminophen	NSAIDs	Opioids
Side Effects/ Toxicity	Considered relatively safe Liver toxicity in elevated doses	Gastric ulceration/bleeding Decreased renal perfusion Photosensitivity Premature closure of the ductus arteriosus in pregnancy	Respiratory depression Constipation and abdominal pain Urinary retention Sedation N/V Pruritus Confusion (particularly in the elderly) Dependence

Table 16. Opioids

Agent	Relative Dose to Morphine 10 mg IV	Moderate Dose	Onset	Duration	Special Considerations
Codeine	100 mg IV 200 mg PO	15-30 mg PO	Late (30-60 min)	Moderate (4-6 h)	Primarily postoperative use, not for IV use Not ideal, as analgesic effect depends on highly variable CYP2D6 metabolism
Meperidine (Demerol®)	75 mg IV	2-3 mg/kg IV	Moderate (10 min)	Moderate (2-4 h)	Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures Decreased use for pain management due to potential toxicity compared to other opioids. Typically reserved to treat postoperative shivering. Absolute contraindication in patients taking MAO-inhibitors
Morphine	10 mg IV 30 mg PO	0.2-0.3 mg/kg IV 0.4-0.6 mg/kg PO	Moderate (5-10 min)	Moderate (4-5 h)	Histamine release leading to decrease in BP
Morphine Extended Release (e.g M-Eslon®, MS Contin®)	20 mg PO	5-20 mg PO	Late	Long	Do not split, crush, or chew tablet
Oxycodone Controlled Release (Oxyneo®)	20 mg PO	10-20 mg PO (no IV)	Late (30-45 min)	Long (8-12 h)	Do not split, crush, or chew tablet (but can be difficult to swallow)
Oxycodone Regular Tablet (Oxy IR®)	20 mg PO (no IV)	5-15 mg PO	Moderate (15 min)	Moderate (3-6 h)	Percocet® = oxycodone 5 mg + acetaminophen 325 mg
Hydromorphone (Dilaudid®)	1.5-2.0 mg IV 6-8 mg PO	40-60 µg/kg IV 2-4 mg PO	Moderate (15 min)	Moderate (4-5 h)	Less pruritus, N/V, and sedation compared to morphine
Hydromorphone Extended Release (e.g. Hydromorph Contin)	4.0-6.0 mg PO	3-12 mg PO	Late (30-45 min)	Long	Do not split, crush or chew tablet
Fentanyl	100 µg IV	2-3 µg/kg IV	Rapid (<5 min)	Short (0.5-1 h)	Transient muscle rigidity in very high doses
Remifentanil	100 µg IV	0.5-1.5 µg/kg IV	Rapid (1-3 min)	Ultra short (<10 min)	Only use during induction and maintenance of anesthesia
Methadone (opioid agonist)	Morphine to methadone conversion is variable based on patient's morphine dose. Ranges from 1/4 to 1/20	15-40 mg/d in divided doses	Rapid (8 min)	15-90 h (24 h average)	Can only be prescribed by federally/provincially licensed physicians and nurse practitioners Acts through both NMDA and µ-opioid receptors Challenging due to variable equianalgesic dose and half-life After titration, accumulates in tissue for once/twice daily dosing Metabolized by CYP3A4 Caution with high doses, may cause QT prolongation, baseline ECG required
Buprenorphine (opioid agonist antagonist)	Varies depending on route of administration (pill/film, transdermal)	Film: 2 mg up to max of 24 mg	Moderate-to-severe (30 min)	6-8 h	For moderate to severe chronic pain and opioid addiction Ceiling effect for respiratory depression but not analgesia High affinity to µ-opioid receptors, very resistant to reversal with opioid antagonists

In general, parenteral route is 2-3x more potent than oral

Opioid Conversion

	Parenteral (IV)	Equivalent Oral Dose
Morphine	10 mg	30 mg
Hydromorphone	2 mg	4 mg
Codeine	120 mg	200 mg
Oxycodone	N/A	20 mg
Fentanyl	100 µg	N/A

Patient Controlled Analgesia

- use of computerized pumps to deliver a constant infusion and bolus breakthrough doses of parenterally-administered opioid analgesics
- limited by lockout intervals
- most commonly used agents: morphine and hydromorphone
- see *Table 17, A27* for suggested infusion rate, PCA dose, and lockout intervals

PCA Parameters

- Loading dose
- Bolus dose
- Lockout interval
- Continuous infusion (optional)
- Maximum 4h dose (limit)

Advantages of PCA

- Improved patient satisfaction
- Fewer side effects
- Accommodates patient variability
- Accommodates changes in opioid requirements

Table 17. Opioid PCA Doses

Agent	PCA Dose	PCA Lockout Interval	PCA 4 h Maximum
Morphine	1-2 mg	5 min	30 mg
Hydromorphone	0.2-0.4 mg	5 min	10 mg
Fentanyl	25-50 µg	5 min	400 µg

Opioid Antagonists (naloxone, naltrexone)

- indication: opioid overdose (manifests primarily at CNS, e.g. respiratory depression)
- mechanism of action: competitively inhibit opioid receptors, predominantly µ-opioid receptors
  - naloxone is short-acting ($t_{1/2}$ = 1 h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
  - naltrexone is longer acting ($t_{1/2}$ = 10 h); less likely to see return of opioid effects
- side effects: relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, HTN, re-emergence of pain, pulmonary edema, and seizures (essentially opioid withdrawal)

Neuropathic Pain

- see Neurology, N43

Chronic Pain

- chronic pain: pain greater than 3 mo, or recurrent pain that occurs at least 3 times throughout 3 mo period
- pain of duration or intensity that persists beyond normal tissue healing and adversely affects functioning
- in the perioperative period, consider continuing regular long-acting analgesics and augmenting with regional techniques, adjuvants, additional opioid analgesia, and non-pharmacological techniques (e.g. mindfulness, physiotherapy, acupuncture)

Central Sensitization

- central sensitization: hyperalgesia (i.e. increased sensitivity to pain) as a result of CNS mechanisms
- may have nociceptive and neuropathic components; dysregulation of analgesic pathways implicated
- plays a role in fibromyalgia

Chronic Post-Surgical Pain

- pain that develops after surgery and persists for at least 2 mo
- primary predictor is history of chronic pain; other risk factors include female gender, surgical procedure/approach, poor social supports, catastrophizing behaviour

Obstetrical Anesthesia

Anesthesia Considerations in Pregnancy

- **airway**
  - possible difficult airway as tissues becomes edematous and friable, especially in labour
- **respiratory system**
  - decreased FRC and increased O_2 consumption cause more rapid desaturation during apnea
- **cardiovascular system**
  - increased blood volume > increased RBC mass results in mild anemia
  - decreased SVR proportionately greater than increased CO results in decreased BP
  - prone to decreased BP due to aortocaval compression (supine hypotensive syndrome) – a pregnant patient is positioned in left uterine displacement (approximately 15° - angle) using a wedge under right flank when supine
- **central nervous system**
  - decreased MAC due to hormonal effects
  - increased block height due to engorged epidural veins
- **gastrointestinal system**
  - delayed gastric emptying
  - increased volume and acidity of gastric fluid
  - decreased LES tone
  - increased abdominal pressure
  - combined, these lead to an increased risk of aspiration; therefore, for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity

Options for Analgesia during Labour

- psychoprophylaxis – Lamaze method
  - patterns of breathing and focused attention on fixed object

Patient Controlled Opioid Analgesia vs. Non-Patient Controlled Opioid Analgesia for Postoperative Pain
Cochrane DB Syst Rev 2015:CD003348
Purpose: To evaluate the efficacy of patient controlled analgesia (PCA) vs. non-patient controlled opioid analgesia of as-needed opioid analgesia for postoperative pain relief.
Methods: Meta-analyses of RCTs comparing PCA vs. conventional administration of opioid analgesia. Assessment employed a visual analog scale (VAS) for pain intensity along with overall analgesic consumption, patient satisfaction, length of stay, and adverse side effects.
Results: 49 studies with a total of 1725 patients receiving PCA and 1687 patients assigned to a control group. PCA had a lower VAS pain intensity score vs. non-patient controlled analgesia over most time intervals in the first 48 h. PCA was associated with higher patient satisfaction and consumed higher amounts of opioids than controls. PCA was also associated with higher incidence of pruritus but not other adverse events.
Conclusions: Moderate to low quality evidence that PCA is an efficacious alternative to non-patient controlled systemic analgesia for postoperative pain control.

Nociceptive Pathways in Labour and Delivery
Labour
Cervical dilation and effacement stimulates visceral nerve fibres entering the spinal cord at T10-L1
Delivery
Distention of lower vagina and perineum causes somatic nociceptive impulses via the pudendal nerve entering the spinal cord at S2-S4

Epidural vs. Non-Epidural or No Analgesia for Pain Management in Labour
Cochrane DB Syst Rev 2018:CD000331
Purpose: To assess effectiveness and safety of all types of epidural analgesia when compared with non-epidural or no pain relief during labour.
Methods: Systematic review of RCTs comparing epidural with any form of pain relief not involving regional blockade, or no pain relief in labour.
Results: 52 studies involving over 11000 women were included; 34 studies compared epidural analgesia with opioids. Epidural analgesia was associated with lower pain intensity, higher satisfaction, and decreased need for additional pain relief vs. opioids. While it was also associated with increased risk of assisted vaginal birth (RR 1.44, 95% CI 1.29-1.60), post-hoc analysis of studies conducted after 2005 eliminates this risk (RR 1.19, 95% CI 0.97-1.46). Women with epidural analgesia experienced more hypotension, motor blockage, fever, and urinary retention with less risk of respiratory depression and nausea/vomiting. There was no difference in neonatal outcomes, admission to NICU, caesarean section rates, or maternal long-term backache.
Conclusions: Epidural analgesia may be more effective in reducing pain during labour and increasing maternal satisfaction than non-epidural methods and, when considering modern approaches, is not associated with increased instrumentation. Epidural analgesia had no impact on the risk of caesarean section or long-term backache, and did not appear to have an immediate effect on neonatal status as determined by Apgar scores or in admissions to NICU.

- systemic medication
  - easy to administer, but risk of maternal or neonatal respiratory depression
  - opioids most commonly used if delivery is not expected within 4 h; fentanyl can be considered
- inhalational analgesia
  - easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
  - nitrous oxide 50% is insufficient alone but good safety profile for mother and child
- neuraxial anesthesia
  - provides excellent analgesia with minimal depressant effects
  - hypotension is the most common complication
  - maternal BP monitored q2-5 min for 15-20 min after initiation and regularly thereafter
  - epidural usually given as it preferentially blocks sensation, leaving motor function intact

Options for Cesarean Section

- neuraxial: spinal or epidural
- general: used if contraindications or time precludes regional blockade (see *Regional Anesthesia, Epidural and Spinal Anesthesia, A21*)

Pediatric Anesthesia

Respiratory System

- in comparison to adults, anatomical differences in infants include:
  - large head, short trachea/neck, large tongue, larynx positioned more superior and anterior, adenoids, and tonsils
  - narrow nasal passages (obligate nasal breathers until 5 mo)
  - narrowest part of airway at the level of the cricoid vs. glottis in adults
  - epiglottis is longer, U-shaped and angled at 45°; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include:
  - faster respiratory rate, immature respiratory centres that are depressed by hypoxia/hypercapnia (airway closure occurs in the neonate at the end of expiration)
  - less O_2 reserve during apnea – decreased total lung volume, vital capacity, and FRC together with higher metabolic needs
  - to increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume
  - neonate: 30-40 breaths/min
  - age 1-13: (24 – [age/2]) breaths/min
  - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm, and higher resistance to airflow

Cardiovascular System

- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume is lost
- children have a high HR and low BP
- CO is dependent on HR, not SV because of low heart wall compliance; therefore, bradycardia severely compromises CO

Temperature Regulation

- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant's head, humidification of inspired gases, and warming of infused solutions

Central Nervous System

- MAC of halothane is increased compared to the adult (0.75% adult, 1.2% infant, 0.87% neonate)
- NMJ is immature for the first 4 wk of life, and thus, there is an increased sensitivity to non-depolarizing relaxants
- parasympathetics mature at birth, sympathetics mature at 4-6 mo; thus, there is an autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

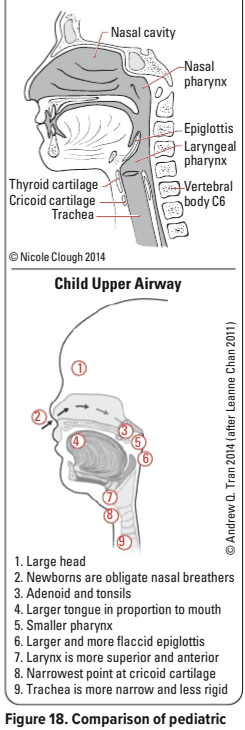
Glucose Maintenance

- infants <1 yr can become seriously hypoglycemic during preoperative fasting and postoperatively if feeding is not recommenced as soon as possible
- after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

Pharmacology

- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB

Techniques for Preventing Hypotension During Spinal Anaesthesia for Cesarean Section
Cochrane DB Syst Rev 2017;8:CD002251
Purpose: To assess the effects of prophylactic interventions for maternal hypotension following spinal anesthesia for caesarean section.
Methods: Searched Cochrane Pregnancy and Childbirth's Trials Register and reference lists. Included RCTs comparing interventions to prevent hypotension with placebo or alternative treatment.
Results: 126 studies were included involving 9565 participants. Identified 3 intervention groups which were IV fluids (colloid vs. crystalloid vs. no fluid), pharmacological interventions (ephedrine vs. phenylephrine, or ondansetron vs. control), and physical interventions (lower limb compression, or lying vs. walking). All groups showed better control of hypotension with no differences between colloid vs. crystalloid, ephedrine vs. phenylephrine, or lying vs. walking. All evidence was very-low quality to low-quality.
Conclusions: While interventions such as crystalloids, colloids, ephedrine, phenylephrine, ondansetron, or lower leg compression can reduce the incidence of hypotension, none have been shown to be superior to the other.



1. Large head
2. Newborns are obligate nasal breathers
3. Adenoid and tonsils
4. Larger tongue in proportion to mouth
5. Smaller pharynx
6. Larger and more flaccid epiglottis
7. Larynx is more superior and anterior
8. Narrowest point at cricoid cartilage
9. Trachea is more narrow and less rigid

Figure 18. Comparison of pediatric vs. adult airway

See Landmark Anesthesiology Trials table for more information on the WOMAN trial, which determines the effects of early tranexamic acid administration on death, hysterectomy, and other relevant outcomes in women with postpartum hemorrhage.

- muscle relaxants
  - non-depolarizing
    - immature NMJ, variable response
  - depolarizing
    - must pre-treat with atropine or may experience profound bradycardia and/or sinus node arrest due to PNS > SNS (also dries oral secretions)
    - more susceptible to arrhythmias, hyperkalemia, rhabdomyolysis, myoglobinemia, masseter spasm, and malignant hyperthermia

ETT Sizing in Pediatrics
Diameter (mm) of tracheal tube in children after 1 year = (age/4) + 4
Length (cm) of tracheal tube = (age/2) + 12

See Landmark Anesthesiology Trials table for more information on a study by Sun et al., 2016 , which details the association between a single general anesthesia exposure prior age 36 months and neurocognitive outcomes in later childhood.

Uncommon Complications

Malignant Hyperthermia

- hypermetabolic disorder of skeletal muscle
- due to an uncontrolled increase in intracellular Ca $^{2+}$ (because of an anomaly of the ryanodine receptor that regulates Ca^{2+} channel in the sarcoplasmic reticulum of skeletal muscle)
- autosomal dominant inheritance
- incidence of 1-5 in 100000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH include:
  - all inhalational agents except nitrous oxide
  - depolarizing muscle relaxants: SCh

Signs of Malignant Hyperthermia
unexplained rise in $ETCO_2$
increase in minute ventilation
tachycardia
rigidity
hyperthermia (late sign)

Clinical Picture

- onset: immediate or hours after contact with trigger agent
  - increased O_2 consumption
  - increased $ETCO_2$ on capnograph
  - tachycardia/dysrhythmia
  - tachypnea/cyanosis
  - diaphoresis
  - HTN
  - hyperthermia (late sign)
- muscular symptoms
  - trismus (i.e. masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  - tender, swollen muscles due to rhabdomyolysis
  - trunk or total body rigidity

Basic Principles of MH Management

"Some Hot Dude Better Get Iced Fluids Fast"
Stop all triggering agents, give 100% O_2
Hyperventilate
Dantrolene 2.5 mg/kg q5 min
Bicarbonate
Glucose and insulin
IV fluids; cool patient to 38°C
Fluid output; consider furosemide
Fast Heart [tachycardia]; be prepared to treat VT

Complications

- coma
- DIC
- rhabdomyolysis
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema
- can be fatal if untreated

Prevention

- suspect MH in patients with a family history of problems/death with anesthetic
- avoid all trigger medications, use vapour-free equipment, use regional anesthesia if possible
- central body temp and ETCO $_2$ monitoring

Malignant Hyperthermia Management

Based on Malignant Hyperthermia Association of the U.S. [MHAUS] Guidelines, 2008

1. notify surgeon, discontinue volatile agents and SCh, hyperventilate with 100% O_2 at flows of 10 L/min or more, halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
   - repeat until there is control of signs of MH; up to 30 mg/kg as necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis
4. cool patients with core temperature >39°C
   - lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
   - stop cooling if temperature is <38°C to prevent drift to <36°C
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
   - use standard drug therapy except Ca^{2+} channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene

6. hyperkalemia
   - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
   - bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg, or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia and check glucose levels hourly
7. follow $ETCO_2$, electrolytes, blood gases, CK, core temperature, urine output/colour with Foley catheter, coagulation studies
   - if CK and/or potassium rises persistently or urine output falls to <0.5 mL/kg/h, induce diuresis to >1 mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids, and propofol
9. transfer to ICU bed

Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- individuals with abnormal pseudocholinesterase will have prolonged muscular blockade
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors as it will cause rebound neuromuscular blockade once cholinesterase inhibitor effect is terminated)

Appendices

Difficult Tracheal Intubation in Unconscious Patient

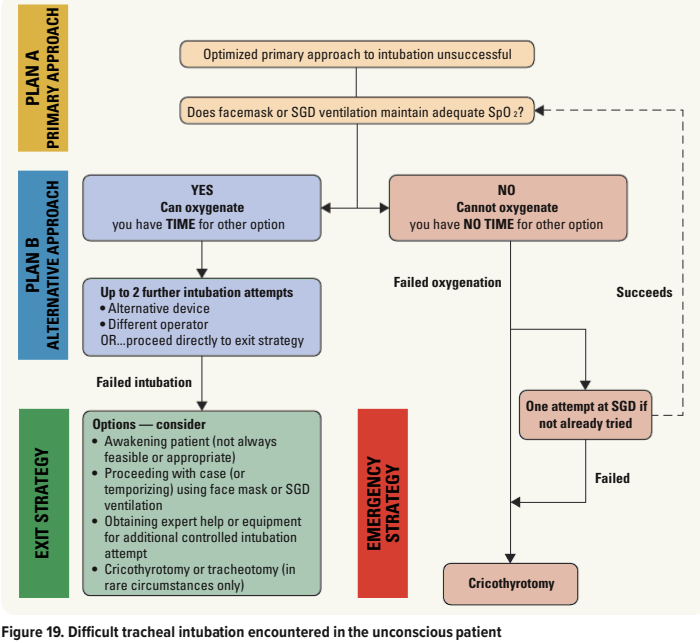

PLAN A
PRIMARY APPROACH
Optimized primary approach to intubation unsuccessful
Does facemask or SGD ventilation maintain adequate SpO2?
PLAN B
ALTERNATIVE APPROACH
YES
Can oxygenate
you have TIME for other option
NO
Cannot oxygenate
you have NO TIME for other option
Failed oxygenation
Succeeds
Up to 2 further intubation attempts
• Alternative device
• Different operator
OR...proceed directly to exit strategy
Failed intubation
One attempt at SGD if not already tried
Failed
EXIT STRATEGY
Options — consider
• Awakening patient (not always feasible or appropriate)
• Proceeding with case (or temporizing) using face mask or SGD ventilation
• Obtaining expert help or equipment for additional controlled intubation attempt
• Cricothyrotomy or tracheotomy (in rare circumstances only)
EMERGENCY STRATEGY
Cricothyrotomy

Figure 19. Difficult tracheal intubation encountered in the unconscious patient
SGD = supraglottic device

Reprinted with permission. Law JA, Broemling N, Copper RM, et al. The difficult airway with recommendations for management – Part 1 – Difficult tracheal intubation encountered in an unconscious/induced patient. Can J Anesth 2013;60:1089–1118.

Difficult Tracheal Intubation

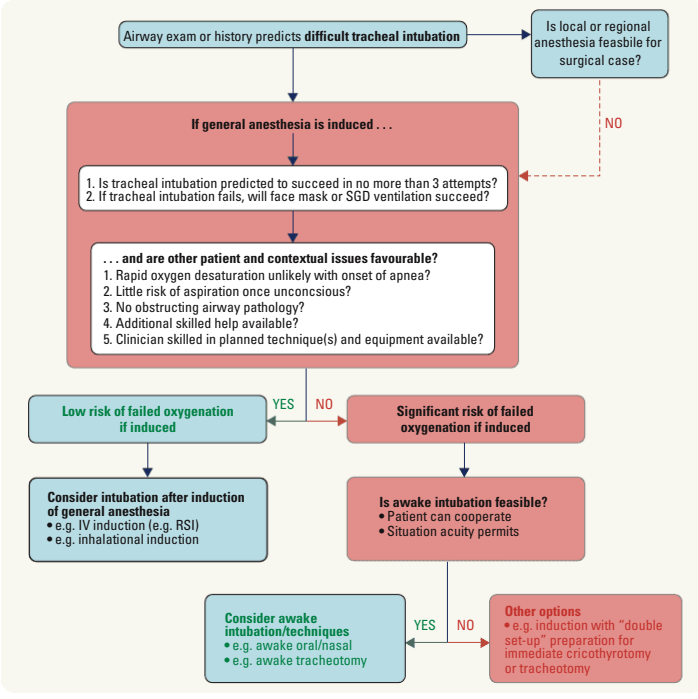

Airway exam or history predicts **difficult tracheal intubation**
Is local or regional anesthesia feasbile for surgical case?
NO
If general anesthesia is induced . . .
1. Is tracheal intubation predicted to succeed in no more than 3 attempts?
2. If tracheal intubation fails, will face mask or SGD ventilation succeed?
. . . and are other patient and contextual issues favourable?
1. Rapid oxygen desaturation unlikely with onset of apnea?
2. Little risk of aspiration once unconcsious?
3. No obstructing airway pathology?
4. Additional skilled help available?
5. Clinician skilled in planned technique(s) and equipment available?
Low risk of failed oxygenation if induced
YES
NO
Significant risk of failed oxygenation if induced
Consider intubation after induction of general anesthesia
• e.g. IV induction (e.g. RSI)
• e.g. inhalational induction
Is awake intubation feasible?
• Patient can cooperate
• Situation acuity permits
Consider awake intubation/techniques
• e.g. awake oral/nasal
• e.g. awake tracheotomy
YES
NO
Other options
• e.g. induction with "double set-up" preparation for immediate cricothyrotomy or tracheotomy

Figure 20. Anticipated difficult tracheal intubation
SGD = supraglottic device

Reprinted with permission: Law JA, Broemling N, Copper RM, et al. The difficult airway with recommendations for management – Part 2 – The anticipated difficult airway. Can J Anesth 2013;60:1119-1138.

Advanced Cardiac Life Support Guidelines

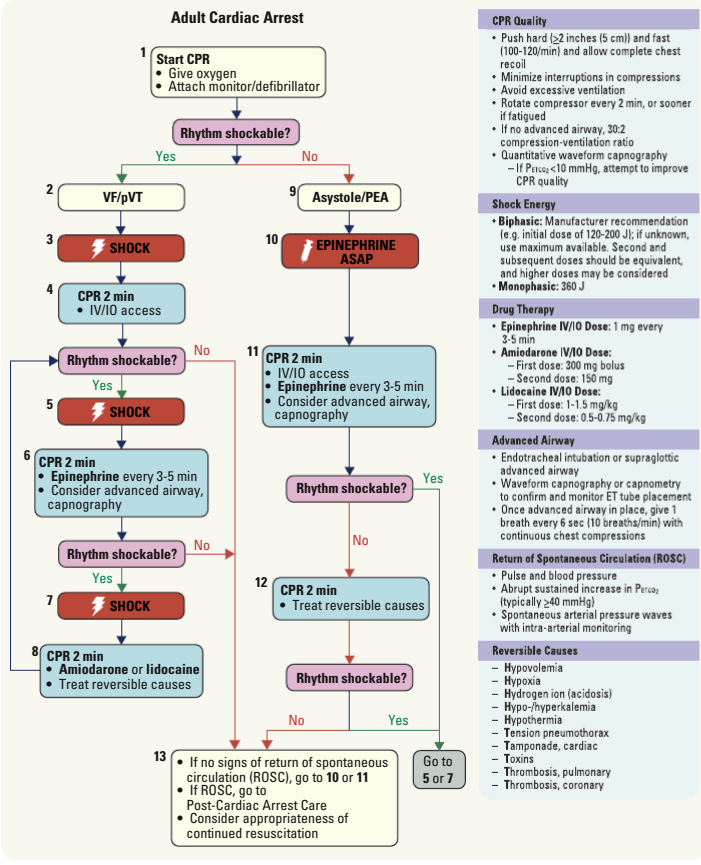

Adult Cardiac Arrest
1 Start CPR
• Give oxygen
• Attach monitor/defibrillator
Rhythm shockable?
Yes
No
2 VF/pVT
3 SHOCK
4 CPR 2 min
• IV/IO access
Rhythm shockable?
No
Yes
5 SHOCK
6 CPR 2 min
• Epinephrine every 3-5 min
• Consider advanced airway, capnography
Rhythm shockable?
No
Yes
7 SHOCK
8 CPR 2 min
• Amiodarone or lidocaine
• Treat reversible causes
9 Asystole/PEA
10 EPINEPHRINE ASAP
11 CPR 2 min
• IV/IO access
• Epinephrine every 3-5 min
• Consider advanced airway, capnography
Rhythm shockable?
Yes
No
12 CPR 2 min
• Treat reversible causes
Rhythm shockable?
No
Yes
13
• If no signs of return of spontaneous circulation (ROSC), go to 10 or 11
• If ROSC, go to Post-Cardiac Arrest Care
• Consider appropriateness of continued resuscitation
Go to 5 or 7
CPR Quality
• Push hard (≥2 inches (5 cm)) and fast (100-120/min) and allow complete chest recoil
• Minimize interruptions in compressions
• Avoid excessive ventilation
• Rotate compressor every 2 min, or sooner if fatigued
• If no advanced airway, 30:2 compression-ventilation ratio
• Quantitative waveform capnography
– If PETCO2 <10 mmHg, attempt to improve CPR quality
Shock Energy
• Biphasic: Manufacturer recommendation (e.g. initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered
• Monophasic: 360 J
Drug Therapy
• Epinephrine IV/IO Dose: 1 mg every 3-5 min
• Amiodarone IV/IO Dose:
– First dose: 300 mg bolus
– Second dose: 150 mg
• Lidocaine IV/IO Dose:
– First dose: 1-1.5 mg/kg
– Second dose: 0.5-0.75 mg/kg
Advanced Airway
• Endotracheal intubation or supraglottic advanced airway
• Waveform capnography or capnometry to confirm and monitor ET tube placement
• Once advanced airway in place, give 1 breath every 6 sec (10 breaths/min) with continuous chest compressions
Return of Spontaneous Circulation (ROSC)
• Pulse and blood pressure
• Abrupt sustained increase in PETCO2 (typically ≥40 mmHg)
• Spontaneous arterial pressure waves with intra-arterial monitoring
Reversible Causes
– Hypovolemia
– Hypoxia
– Hydrogen ion (acidosis)
– Hypo-/hyperkalemia
– Hypothermia
– Tension pneumothorax
– Tamponade, cardiac
– Toxins
– Thrombosis, pulmonary
– Thrombosis, coronary

Figure 21. Adult cardiac arrest algorithm

Reprinted with permission: Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020;142:S366-S468.

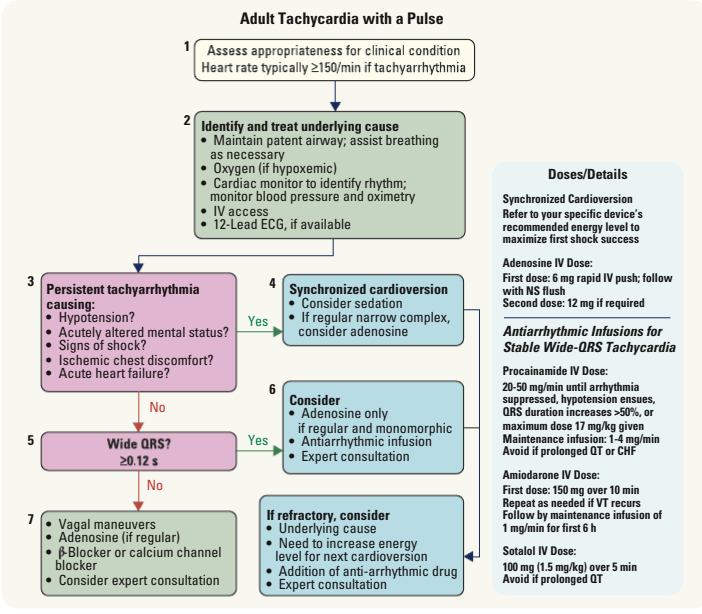

Adult Tachycardia with a Pulse
1
Assess appropriateness for clinical condition
Heart rate typically ≥150/min if tachyarrhythmia
2
Identify and treat underlying cause
• Maintain patent airway; assist breathing as necessary
• Oxygen (if hypoxemic)
• Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
• IV access
• 12-Lead ECG, if available
3
Persistent tachyarrhythmia causing:
• Hypotension?
• Acutely altered mental status?
• Signs of shock?
• Ischemic chest discomfort?
• Acute heart failure?
Yes
4
Synchronized cardioversion
• Consider sedation
• If regular narrow complex, consider adenosine
No
5
Wide QRS? ≥0.12 s
Yes
6
Consider
• Adenosine only if regular and monomorphic
• Antiarrhythmic infusion
• Expert consultation
No
7
• Vagal maneuvers
• Adenosine (if regular)
• β-Blocker or calcium channel blocker
• Consider expert consultation
If refractory, consider
• Underlying cause
• Need to increase energy level for next cardioversion
• Addition of anti-arrhythmic drug
• Expert consultation
Doses/Details
Synchronized Cardioversion
Refer to your specific device's recommended energy level to maximize first shock success
Adenosine IV Dose:
First dose: 6 mg rapid IV push; follow with NS flush
Second dose: 12 mg if required
Antiarrhythmic Infusions for Stable Wide-QRS Tachycardia
Procainamide IV Dose:
20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases >50%, or maximum dose 17 mg/kg given
Maintenance infusion: 1-4 mg/min
Avoid if prolonged QT or CHF
Amiodarone IV Dose:
First dose: 150 mg over 10 min
Repeat as needed if VT recurs
Follow by maintenance infusion of 1 mg/min for first 6 h
Sotalol IV Dose:
100 mg (1.5 mg/kg) over 5 min
Avoid if prolonged QT

Figure 22. Adult tachycardia with a pulse algorithm

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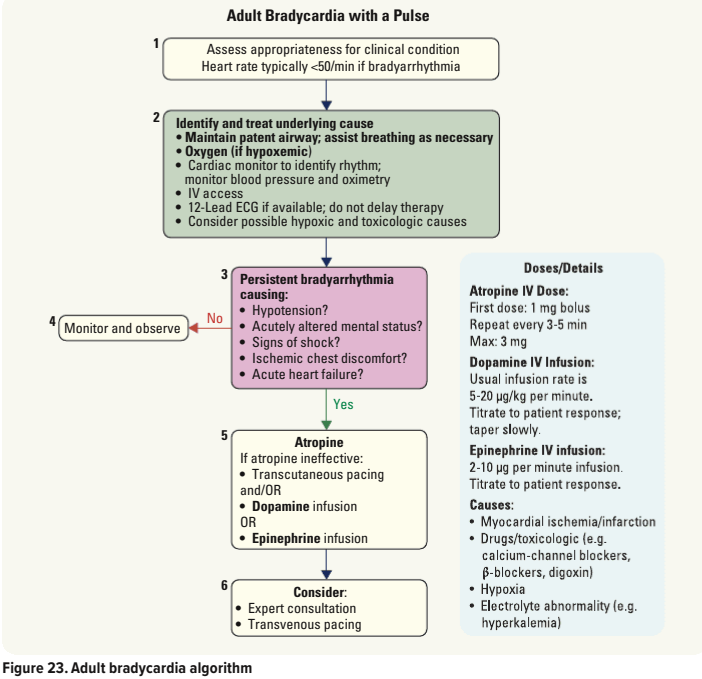

Figure 23. Adult bradycardia algorithm

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Landmark Anesthesiology Trials

Trial Name	Reference	Clinical Trial Details
INTRAOPERATIVE MANAGEMENT		
MYRIAD	NEJM 2019;380:1214-1225	**Title:** Volatile Anesthetics vs. Total Intravenous Anesthesia (TIVA) for Cardiac Surgery **Purpose:** Volatile agents have cardioprotective effects which could improve clinical outcomes in cardiac surgery patients. **Methods:** Multicenter, single-blind, controlled trial. Patients scheduled to undergo elective CABG were randomly assigned to an intraoperative anesthetic regimen that included a volatile anesthetic (desflurane, isoflurane, or sevoflurane) or to TIVA. The primary outcome was all-cause mortality at 1 yr. **Results:** A total of 5400 patients were randomized. No significant difference between the groups with respect to all-cause mortality was seen at 1 yr (2.8% in the volatile anesthetics group and 3.0% in the TIVA group; RR, 0.94; 95% CI, 0.69 to 1.29; P=0.71), or at 30 d (1.4% and 1.3%, respectively; RR, 1.11; 95% CI, 0.70 to 1.76). There were no significant differences between the groups in any of the secondary outcomes or in the incidence of prespecified adverse events, including MI. **Conclusion:** Among patients undergoing elective CABG, anesthesia with a volatile agent did not result in significantly fewer deaths at 1 yr than TIVA.
BAG-RECALL	NEJM 2011;365:591-600	
Study of Wound Infection and Temperature	NEJM 1996; 334:1209-1216	**Title:** Prevention of Intraoperative Awareness in High-Risk Surgical Population **Purpose:** To determine if EEG derived bispectral index (BIS) is superior to a protocol incorporating standard monitoring of end-tidal anesthetic-agent concentration (ETAC) for the prevention of unintended intraoperative awareness. **Methods:** Patients (n=6041) at high risk for awareness were randomly assigned to BIS-guided anesthesia or ETAC-guided anesthesia. **Results:** 0.24% of patients in the BIS group vs. 0.07% of patients in the ETAC group had definite intraoperative awareness (95% CI -0.3 to 0.38, p=0.98). There was no difference between the groups with respect to the amount of anesthesia administered or rate of major postoperative adverse outcomes. **Conclusions:** The superiority of the BIS protocol over the ETAC protocol was not established. Fewer patients in the ETAC group than the BIS group experienced awareness.
POSTOPERATIVE MANAGEMENT		
IMPACT	NEJM 2004; 350:2441-2451	**Title:** A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting **Purpose:** To compare the efficacy of six well-established antiemetic strategies and to determine the extent to which efficacy could be improved by combining two or three interventions. **Methods:** Patients (n=5199) were randomly assigned to receive prophylactic antiemetics independently, in combination or placebo. Primary outcome was nausea and vomiting within 24 h after surgery. **Results:** Ondansetron, dexamethasone, and droperidol each reduced risk of postoperative nausea and vomiting by 26%. Propofol reduced risk by 19%, and nitrogen by 12%. Relative risks associated with combined interventions could be estimated by multiplying the relative risks associated with each intervention. Absolute risk reduction was a critical function of patients' baseline risk. **Conclusion:** All interventions were similarly effective and acted independently. The safest or least expensive should be used first. Moderate-risk patients may benefit from a single intervention and high-risk patients from multiple interventions.
DREAMS	BMJ 2017;357:j1455	**Title:** Dexamethasone vs. Standard Treatment for Postoperative Nausea and Vomiting in Gastrointestinal Surgery: Randomised Controlled Trial (DREAMS Trial) **Purpose:** Whether preoperative dexamethasone reduces postoperative nausea and vomiting (PONV) in patients undergoing elective bowel surgery and whether it is associated with other measurable benefits during recovery from surgery. **Method:** Pragmatic two-arm parallel-group randomized trial with blinded postoperative care and outcome assessment. **Results:** Administration of dexamethasone 8 mg IV at induction was associated with lower rates of vomiting within 24 h of surgery (NNT=13) and reduced need for antiemetics up to 72 h (NNT=8) vs. standard of care. **Conclusions:** A single dose of dexamethasone at induction of anesthesia significantly reduces incidence of PONV and need for rescue antiemetics postoperatively with no increase in adverse events.
ENGAGES	JAMA 2019;321:473-483	**Title:** Effect of EEG-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES RCT **Purpose:** To assess whether EEG-guided anesthetic administration decreases the incidence of postoperative delirium. **Methods:** RCT of 1232 adults >60 yr old undergoing major surgery and receiving guided anesthetic. Patients randomized 1:1 to receive EEG-guided anesthetic administration or usual care. Primary outcome was incident delirium during postoperative days 1-5. **Results:** Delirium during postoperative days 1-5 occurred in 26.0% of the guided group and in 23.0% of the usual care group (P = .22). Median end-tidal volatile anesthetic concentration was significantly lower in the guided group than the usual care group, and median cumulative time with EEG suppression was significantly less (7 vs. 13 min; difference, -6.0 [95% CI, -9.9 to -2.1]). **Conclusion:** There is no difference in postoperative delirium between EEG-guided anesthetic or usual care of older adults.
COMPLICATIONS		
POISE-3	NEJM 2022;386(21):1986	**Title:** Tranexamic Acid in Patients Undergoing Noncardiac Surgery **Purpose**: To assess the efficacy of tranexamic acid in reducing bleeding in non-cardiac surgery. **Methods**: 9535 patients were randomized to receive tranexamic acid or a placebo during surgery. Life-threatening bleeding, major bleeding, and bleeding into a critical organ were assessed. **Results**: A bleeding event occurred in 433 of 4757 patients in the treatment group as opposed to 561 bleeding events in the placebo group. **Conclusion**: The use of tranexamic acid was shown to significantly reduce the number of bleeding events in non-cardiac surgery.
POISE-3	Ann Intern Med 2023;Epub ahead of print	**Title**: Hypotension-Avoidance Versus Hypertension Avoidance Strategies in Noncardiac Surgery: An International Randomized **Title** Trial **Purpose**: To compare the effects of a hypotension-avoidance and a hypertension-avoidance strategy on major vascular complications after noncardiac surgery. **Methods**: Patients (n=7490) having noncardiac surgery were randomly assigned to the hypotension-avoidance group (intraoperative MAP >80 mmHg, withholding of long-term antihypertensives before and after surgery) or the hypertension-avoidance group (intraoperative MAP >60 mmHg). **Results**: Within 30 days of surgery, 13.9% of the hypotension-avoidance group vs. 14.0% of the hypertension-avoidance group experienced major vascular complications (composite of vascular death and nonfatal myocardial injury, stroke, cardiac arrest) (HR 0.99, 95% CI 0.88 to 1.12, P=0.92). **Conclusion**: In patients having noncardiac surgery, there are similar incidences of major vascular complications using hypotension-avoidance and hypertension-avoidance strategies.

Trial Name	Reference	Clinical Trial Details
POISE-2	NEJM 2014;370:1504-1513	**Title**: Clonidine in Patients Undergoing Noncardiac Surgery **Purpose**: To evaluate low-dose clonidine vs. placebo in patients having noncardiac surgery. **Methods**: Patients (n=10,010) with or at risk for atherosclerotic disease were randomly assigned to receive clonidine or placebo just before surgery. **Results**: Clonidine did not reduce the rate of death or nonfatal MI 30 days post-surgery. Clonidine increased clinically important hypotension (47.6% vs. 37.1%, HR 1.32, 95% CI 1.24 to 1.40, pP<0.001) and nonfatal cardiac arrest (0.3% vs. 0.1%, HR 3.20, 95% CI 1.17 to 8.73, pP=0.02). **Conclusion**: Clonidine does not reduce the rate of death and non-fatal MI, but does increase the risk of hypotension and nonfatal cardiac arrest.
POISE-2	NEJM 2014;370:1491-1503	**Title**: Aspirin in Patients Undergoing Noncardiac Surgery **Purpose**: To evaluate low-dose aspirin vs. placebo in patients having noncardiac surgery **Methods**: Patients (n=10,010) preparing to undergo noncardiac surgery and at risk for vascular complications were randomly assigned to receive aspirin or placebo. **Results**: Death and nonfatal MI occurred in 7.0% in the aspirin group and in 7.1% of patients in the placebo group (HR 0.99, 95% CI 0.86 to 1.15, pP=0.92) 30 days post-surgery. Major bleeding was more common in the aspirin group than the placebo group (4.6% vs. 3.8%, HR 1.23, 95% CI 1.01 to 1.49, P=0.04). **Conclusion**: Aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal MI but increased the risk of major bleeding.
POISE	Lancet 2008;371:1839-1847	**Title**: Effects of Extended-Release Metoprolol Succinate in Patients Undergoing Non-cardiac Surgery (POISE trial): A Randomized Controlled Trial **Purpose**: To investigate the effects of perioperative β blockers. **Methods**: Patients (n=8351) with or at risk of atherosclerotic disease having non-cardiac surgery were randomly assigned to receive extended release metoprolol succinate or placebo. **Results**: 5.8% of the metoprolol group vs. 6.9% in the placebo group had a major cardiovascular event (HR 0.84, 95% CI 0.70 to 0.99, P=0.0399). The metoprolol group had lower incidences of MI (4.2% vs. 5.7%, P=0.0017), but had higher incidences of death (3.1% vs. 2.3%, P=0.0317) and stroke (1.0% vs. 0.5%, P=0.0053). **Conclusion**: Perioperative β blockers have benefit without substantial harm. Patients are unlikely to accept the associated risks.
PROTECT	Lancet2022;399(10337):1799-1808	Ti **Title** tle: Aggressive Intraoperative Warming versus Routine Thermal Management during Non-Cardiac Surgery (PROTECT): A Multicentre, Parallel Group, Superiority Trial **Purpose**: To determine if aggressive intraoperative warming reduces major perioperative complications. **Methods**: Patients (n=5013) having non-cardiac surgery were randomly assigned to receive either aggressive warming to a target core temperature of 37°C or routine thermal management to a target of 35.5°C. **Results**: The primary outcome (MI, cardiac arrest, or mortality) occurred in 9.9% of patients in the aggressively warmed group vs. 9.6% in the routine thermal management group. The common relative risk of aggressive vs. routine thermal management was an estimated 1.04 (95% CI 0.87 to 1.27, P=0.69). **Conclusion**: The incidence of major cardiovascular complications did not differ significantly in the aggressively warmed or routine thermal management group.
GAS	Lancet 2019;393:664-677	**Title**: Neurodevelopmental Outcome at 5 Years of Age After General Anesthesia or Awake-Regional Anesthesia in Infancy (GAS): An International Multicentre, Randomized, Controlled Equivalence Trial **Purpose**: To determine if general anesthesia in early infancy affects neurodevelopmental outcomes. **Methods**: Infants (n=722) undergoing inguinal herniorrhaphy without risk factors for neurological injury were randomly assigned to receive awake-regional anesthetic or sevoflurane-based GA. **Results**: Full scale intelligence quotient score at 5 yr was 99.08 (SD 18.35) in the awake-regional anesthesia group and 98.97 (SD 19.66) in the general anesthesia group, with a difference in means (awake-regional anesthesia minus general anesthesia) of 0.23 (95% CI -2.59 to 3.06). **Conclusion**: Less than 1 hr of GA in early infancy does not alter neurodevelopmental outcome compared to awake-regional anesthesia.
BALANCEDLT	Lancet 2019;394(10212):1901-1914	**Title**: Anesthetic Depth and Complications After Major Surgery: An International, Randomized Controlled Trial **Purpose**: To compare all-cause-1yr mortality in older patients having major surgery and randomly assigned to light (BIS target 50) or deep (BIS target 35) general anesthesia. **Methods**: Patients (n=6644) at high risk of complications after major surgery were randomly assigned to receive light general anesthesia or deep general anesthesia. **Results**: 1 yr mortality was 6.5% in the deep anesthesia group and 7.2% in the light anesthesia group (HR 0.88, 95% CI 0.73 to 1.07, absolute risk reduction 0.8%, 95% CI -0.5 to 2.0. **Conclusion**: Light anesthesia was not associated with lower 1-year mortality than deep general anesthesia.
RELIEF	NEJM 2018;378:2263-2274	**Title**: Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery **Purpose**: To assess a restrictive IV fluid strategy for patients having major abdominal surgery. **Methods**: Patients (n=3000) with an increased risk of complications were randomly assigned to receive a restrictive or liberal IV fluid regimen during and up to 24 h after surgery **Results**: The rate of disability-free survival at 1 yr was 81.9% in the restrictive fluid group and 82.3% in the liberal fluid group (HR 1.05, 95% CI 0.88 to 1.24, p=0.61). The rate of acute kidney injury was 8.6% in the restrictive fluid group and 5.0% in the liberal fluid group (P<0.001). **Conclusion**: Restrictive fluid regimen was not associated with higher.
WOMAN	Lancet 2017;389:2105-2116	**Title**: Effect of Early Tranexamic Acid Administration on Mortality, Hysterectomy, and Other Morbidities in Women with Post-Partum Hemorrhage (WOMAN): An International, Randomized, Double-blind, Placebo-controlled Trial **Purpose**: To determine the effects of early administration of tranexamic acid (TXA) on death, hysterectomy, and other relevant outcomes in women with postpartum hemorrhage. **Methods**: Patients (n=20,060) with a clinical diagnosis of postpartum hemorrhage after a vaginal birth or cesarean section were randomly assigned to receive TXA or placebo in addition to usual care. **Results**: Death due to bleeding was significantly reduced in TXA group (1.5% vs. 1.9%, RR 0.81, 95% CI 0.65 to 1.00, pP=0.045), especially if given within 3 hr of giving birth (1.2% vs. 1.7%, RR 0.69, 95% CI 0.52 to 0.91, pP=0.008). All other causes of death or thromboembolic events did not differ significant. **Conclusion**: TXA reduces death due to bleeding in women with postpartum hemorrhage and should be given as soon as possible after bleeding onset.
ENIGMA-II	Lancet 2014;384(9952):1446-1454	**Title**: The Safety of Addition of Nitrous Oxide to General Anesthesia in at-risk Patients Having a Major Non-cardiac Surgery (ENIGMA-II): A Randomized, Single-Blind Trial Purpose: To determine if nitrous oxide (NO) affects perioperative cardiovascular risk. **Methods**: Patients (n=7112) with known or suspected CAD undergoing noncardiac surgery were randomly assigned to receive NO or NO-free anesthesia. **Results**: Cardiovascular complications occurred in 8% of patients receiving NO and in 8% of patients in the NO-free group (RR 0.96, 95% CI 0.83 to 1.12, P=0.64) within 30 days of surgery. Surgical site infection (SSI) occurred in 9% of patients receiving NO and in 9% of NO-free patients (P=0.61). **Conclusions**: NO did not increase the risk of death, cardiovascular complications, or SSI in major noncardiac surgery.

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Cardiology and Cardiac Surgery

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Acronyms

A	atrium
AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ACEI	angiotensin converting enzyme inhibitor
ACLS	advanced cardiovascular life support
ACS	acute coronary syndrome
ACT	activated clotting time
AFib	atrial fibrillation
AKI	acute kidney injury
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARNI	angiotensin receptor-neprilysin inhibitor
AS	aortic stenosis
ASA	acetylsalicylic acid (Aspirin®)
ASCVD	atherosclerotic cardiovascular disease
ASD	atrial septal defect
AV	atrioventricular
AVNRT	atrioventricular nodal re-entrant tachycardia
AVR	aortic valve replacement
AVRT	atrioventricular reciprocating tachycardia
BIMA	bilateral internal mammary artery
BBB	bundle branch block
BNP	brain natriuretic peptide
BPM	beats per minute
BiVAD	biventricular assist device
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCB	calcium channel blocker
CHD	coronary heart disease
CM	cardiomyopathy
CMR	cardiovascular magnetic resonance imaging
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CRT	cardiac resynchronization therapy
CRT-P	cardiac resynchronization therapy pacemaker
CRT-D	cardiac resynchronization therapy defibrillator
CV	cardiovascular
CVP	central venous pressure
DCM	dilated cardiomyopathy
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECASA	enteric coated ASA
ECMO	extracorporeal membrane oxygenation
EDP	end diastolic pressure
EF	ejection fraction
EPS	electrophysiology studies
FEV1	forced expiratory volume in the first second
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HFSS	heart failure survival score
HOCM	hypertrophic obstructive cardiomyopathy
HTN	hypertension
ICD	implantable cardioverter-defibrillator
IE	infective endocarditis
IMA	internal mammary artery
ITA	internal thoracic artery
JVP	jugular venous pressure
LA	left atrium
LAD	left anterior descending artery
LAE	left atrial enlargement
LBB	left bundle branch
LBBB	left bundle branch block
LCA	left coronary artery
LCC	left coronary cusp
LCx	left circumflex artery
LIMA	left internal mammary artery
LITA	left internal thoracic artery
LLSB	left lower sternal border
LMWH	low molecular weight heparin
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
MAP	mean arterial blood pressure
MAT	multifocal atrial tachycardia
MI	myocardial infarction
MPI	myocardial perfusion imaging
MR	mitral regurgitation
MS	mitral stenosis
MVD	multivessel coronary artery disease
MVP	mitral valve prolapse
MUGA	multigated acquisition scan
NSR	normal sinus rhythm
NSTEMI	non-ST elevation myocardial infarction
NYHA	New York Heart Association
OMT	optimal medical therapy
OPCAB	off-pump coronary artery bypass
OS	opening snap
PAC	premature atrial contraction
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PCWP	pulmonary capillary wedge pressure
PDA	posterior descending artery
PE	pulmonary embolism
PEA	pulseless electrical activity
PFO	patent foramen ovale
PIV	posterior interventricular artery
PMI	point of maximal impulse
PND	paroxysmal nocturnal dyspnea
PR	pulmonary regurgitation
PS	pulmonary stenosis
PT	pulmonary trunk
PTCA	percutaneous transluminal coronary angioplasty
PUD	peptic ulcer disease
PVC	premature ventricular contraction
PVD	peripheral vascular disease
PVR	pulmonary vascular resistance
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RAE	right atrial enlargement
RBB	right bundle branch
RBBB	right bundle branch block
RCA	right coronary artery
RCC	right coronary cusp
RCM	restrictive cardiomyopathy
RIMA	right internal mammary artery
RITA	right internal thoracic artery
RLSB	right lower sternal border
RF	radiofrequency
RV	right ventricle
RVAD	right ventricular assist device
RVH	right ventricular hypertrophy
RVOT	right ventricular outflow trunk
SA	sinoatrial
SAM	systolic anterior motion
SAVR	surgical aortic-valve replacement
SCD	sudden cardiac death
SEM	systolic ejection murmur
SGLT2	sodium-glucose cotransporter 2
SNS	sympathetic nervous system
SOBOE	shortness of breath on exertion
STEMI	ST elevation myocardial infarction
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
SYNTAX	synergy between percutaneous coronary intervention with taxus and cardiac surgery
TAVI	transcatheter aortic-valve implantation
TAVR	transcatheter aortic-valve replacement
TEE	transesophageal echocardiography
TIA	transient ischemic attack
TR	tricuspid regurgitation
TS	tricuspid stenosis
TTE	transthoracic echocardiography
UA	unstable angina
V	ventricle
VAD	ventricular assist device
VFib	ventricular fibrillation
VHD	valvular heart disease
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
WPW	Wolff-Parkinson-White

Basic Anatomy Review

Coronary Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the aortic sinuses of Valsalva which penetrate the root of the aorta
  - RCA:
    - conus artery
    - acute marginal branches
    - AV nodal artery
    - PDA or PIV
  - LCA:
    - LAD
      - septal branches
      - diagonal branches
    - LCx
      - obtuse marginal branches
- dominance of circulation
  - determined by whether the RCA or the LCx supplies the PDA
    - right-dominant circulation: PDA and at least one posterolateral branch arise from RCA (80%)
    - left-dominant circulation: PDA and at least one posterolateral branch arise from LCx (15%)
    - balanced circulation/codominant: dual supply of posteroinferior LV from RCA and LCx (5%)
- the SA node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
- the AV node is supplied by the AV nodal artery, which may arise from the RCA (90%) or LCx (10%)
- most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through Thebesian veins into all four chambers, contributing to the physiologic R-L shunt

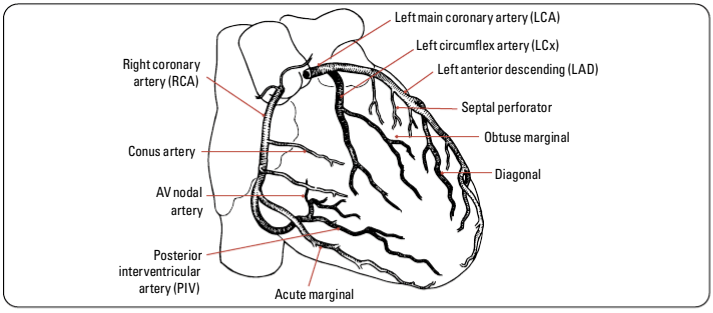

Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)

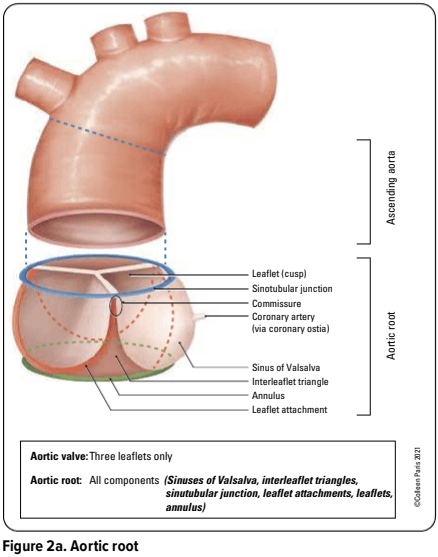

Figure 2a. Aortic root

Modified from Sievers H-H, Hemmer W, The everyday used nomenclature of the aortic root components: the tower of Babel?, European Journal of Cardio-Thoracic Surgery, 2012, 41, 3, 478-82, by permission of Oxford University Press

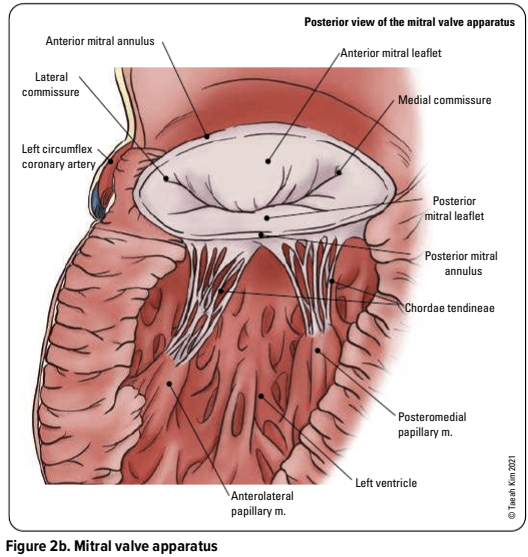

Figure 2b. Mitral valve apparatus

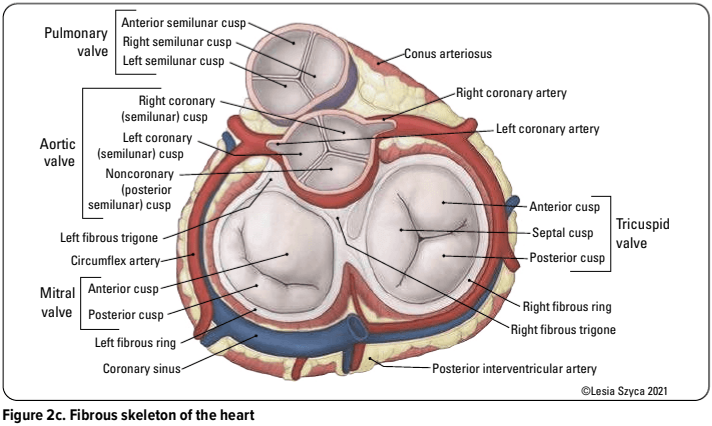

Figure 2c. Fibrous skeleton of the heart

Cardiac Anatomy

- layers of the heart
  - endocardium, myocardium, epicardium, visceral pericardium, pericardial cavity, parietal pericardium
- valves
  - semilunar valves: 3 leaflets separating outflow tracts from the great arteries
    - aortic valve: noncoronary cusp, LCC, RCC; RCC and LCC have coronary ostia; separates LVOT and ascending aorta
    - pulmonary valve: anterior cusp, left cusp, right cusp; separates RVOT and PT
  - atrioventricular valves: subvalvular apparatus present in the form of chordae tendineae and papillary muscles
    - mitral valve: anterior (2/3 valve area, 1/3 valve circumference) and posterior leaflets (1/3 valve area, 2/3 valve circumference); separates LA and LV
    - tricuspid valve: anterior, posterior, and septal leaflets; separates RA and RV
- conduction system
  - SA node
    - located at the junction of the crista terminalis at the opening of the SVC at the roof of the RA
    - governs pace-making; heartbeat originates here
    - anterior-, middle-, and posterior-internal nodal tracts carry impulses in the RA with the atrial impulses converging at the AV node and along Bachmann's bundle in the LA
  - AV node
    - located within the triangle of Koch which is demarcated by: superior margin of the coronary sinus, tendon of Todaro, and hinge of the septal leaflet of the tricuspid valve
    - AV node is the conduit for electrical impulses from atria to ventricles, unless an accessory AV pathway (e.g. WPW syndrome) is present
  - bundle of His
    - AV node connects to the bundle of His, which divides into LBB and RBB
      - LBB further splits into anterior and posterior fascicles
      - RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium

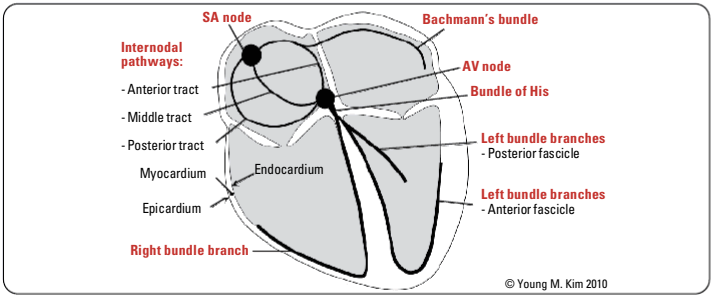

Figure 3. Conduction system of the heart

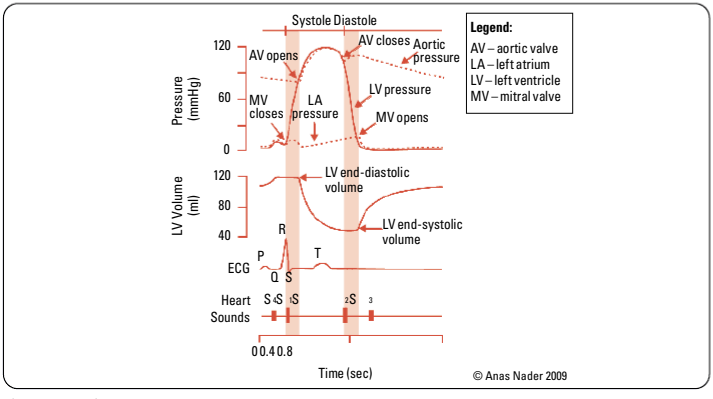

Figure 4. Cardiac cycle
Grey shaded bars indicate isovolumic contraction (left) and isovolumic relaxation (right)

- cardiovascular innervation
  - sympathetic nerves
    - innervate the SA node, AV node, ventricular myocardium, and vasculature
    - increased activity of the SA node via the β1 receptor leads to increased HR via more frequent impulses from pacemaking cells (increased chronotropy - increased HR)
    - cardiac muscle (β1) fibres increase contractility (inotropy - leads to increased SV)
    - stimulation of β1- and β2-receptors in the skeletal and coronary circulation causes vasodilatation
  - parasympathetic nerves
    - innervate the SA node, AV node, and atrial myocardium but few vascular beds
    - at rest, vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node, resulting in slow AV conduction, and consequently a prolonged PR interval or second or third degree AV block (i.e. reduced dromotropy (if only affecting AV node conduction))
    - parasympathetics have very little impact on total peripheral vascular resistance

Differential Diagnoses of Common Presentations

Note: **bold** text indicates most common, underlined text indicates life threatening condition

Chest Pain

- often described as pressure, heaviness, discomfort
  - note: ischemic pain is usually dull and diffuse while chest wall and pericardial pain are often sharp, localized, and worse on inspiration (i.e. pleuritic)
- cardiac
  - MI, stable myocardial ischemia (angina), myocarditis, and pericarditis/Dressler's syndrome, tamponade, and aortic valve disease
- pulmonary
  - PE, pneumothorax/hemothorax, tension pneumothorax, pneumonia, empyema, pulmonary neoplasm, bronchiectasis, pleuritis, asthma, COPD, sarcoidosis, pulmonary hypertension, and tuberculosis
- gastrointestinal
  - esophageal: **GERD**, esophageal rupture, spasm, esophagitis, ulceration, achalasia, neoplasm, and Mallory-Weiss syndrome
  - other structures: PUD, gastritis, pancreatitis, and biliary colic
- mediastinal
  - lymphoma, thymoma
- vascular
  - acute aortic syndrome: aortic dissection, intramural hematoma, penetrating aortic ulcer
- drug use: methamphetamine or cocaine intoxication
- surface structures
- costochondritis
- rib fracture
- skin (bruising, herpes zoster)
- breast
- anxiety/psychosomatic
- referred pain
- trauma

Loss of Consciousness

1. causes of true syncope (impaired cerebral perfusion)

- reflex mediated/reflex dysfunction
  - vasovagal (most common; also known as reflex mediated syncope, neurocardiogenic syncope)
  - situational (micturition, cough, carotid hypersensitivity)
  - autonomic dysfunction (often associated with neurologic diseases)
  - postural hypotension (e.g. central nervous system disorders, antihypertensive drugs)
- inadequate circulating volume (bleeding, hypovolemia with orthostasis)
- obstruction to blood flow
  - tamponade
  - pulmonary embolism
  - severe pulmonary HTN
  - severe obstructive valve disease (MS and AS)
  - left ventricular outflow obstruction (HCM)
  - cerebrovascular events (e.g. cerebrovascular accident)
- arrhythmia leading to sudden loss of CO
  - tachyarrhythmia, (e.g. AFib, SVT, VT, VFib)
  - severe bradycardia (sinus arrest, AV block)

2. loss of consciousness NOT due to impaired cerebral perfusion
- seizure
- hypoglycemia
- severe hypoxia or hypercarbia
- psychiatric
- head trauma

Local Edema

- venous or lymphatic obstruction
  - thrombophlebitis/deep vein thrombosis, venous insufficiency, chronic lymphangitis, lymphatic tumour infiltration, filariasis
- inflammation/infection
- trauma

Generalized Edema

- increased hydrostatic pressure/fluid overload
  - HF, pregnancy, drugs (e.g. CCBs), iatrogenic (e.g. IV fluids)
- decreased oncotic pressure/hypoalbuminemia
  - **liver cirrhosis**, nephrotic syndrome, malnutrition
- increased interstitial oncotic pressure
  - myxedema
- increased capillary permeability
  - severe sepsis
- hormonal
  - hypothyroidism, exogenous steroids, pregnancy, estrogens

Palpitations

- subjective sense of abnormal/irregular heartbeats
- palpitations that may have continuous rapid heart action:
  - conditions causing sinus tachycardia: systemic (fever, inflammation, infection, neoplasm, and autoimmune conditions) endocrine (thyrotoxicosis, pheochromocytoma, and hypoglycemia), haematologic (anemia), drugs (stimulants and anticholinergics), and psychiatric (panic attacks, generalized anxiety disorder, and somatization)
  - conditions causing pathologic tachycardia: SVT (reentrant SVT, atrial tachycardia), atrial fibrillation, and atrial flutter, and VT
- palpitations that may have irregular/intermittent sensations (e.g. PACs, PVCs)

Dyspnea

- exercise
  - elevated pulmonary venous pressure
  - poor Hb-oxygen dissociation curve kinetics
- cardiovascular
  - due to elevated pulmonary venous pressure: acute MI, CHF/LV failure, aortic/mitral stenosis, AS/MS, AR/MR, arrhythmia, and left-sided obstructive lesions (e.g. left atrial myxoma)
  - due to poor cardiac output (cardiac tamponade, constrictive pericarditis, severe TR)
- respiratory
  - airway disease
    - asthma, COPD exacerbation, and upper airway obstruction (anaphylaxis, foreign body, and mucus plugging)
  - parenchymal lung disease
    - pneumonia, interstitial lung disease
  - pulmonary vascular disease
    - PE, pulmonary HTN, and pulmonary vasculitis
  - pleural disease
    - pneumothorax, pleural effusion
- neuromuscular and chest wall disorders
  - cervical spine injury
    - polymyositis, myasthenia gravis, Guillain-Barré syndrome, and kyphoscoliosis
- anxiety/psychosomatic
- hematological/metabolic
  - anemia, acidosis, and hypercapnia

Cardiac Diagnostic Tests

Electrocardiography Basics

Description

- a graphical representation (amplitude of electrical vector projection over time) of the heart's electrical activity
- on the ECG graph
  - the horizontal axis represents time (at usual paper speed of 25 mm/s)
    - 1 mm (1 small square) = 40 msec
    - 5 mm (1 large square) = 200 msec
  - the vertical axis represents voltage (at usual standard gain setting of 10 mm/mV)
    - 1 mm (1 small square) = 0.1 mV
    - 10 mm (2 large squares) = 1 mV
  - standard leads of 12-lead ECG
    - limb (bipolar) leads: I, II, III, aVL, aVR, aVF
    - precordial (unipolar) leads: V1-V6 (V1-V2 (septal), V3-V4 (anterior), and V5-V6 (lateral))
  - additional leads
    - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
    - posterior leads: V7-V9 (useful in posterolateral infarction)
  - leads that indicate specific regions of the heart:
    - lateral wall = I, aVL, V5, V6
    - inferior wall = II, III, aVF
    - anterior wall= V1-V4

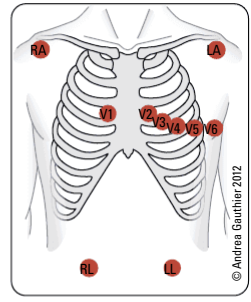

Figure 5. ECG lead placement

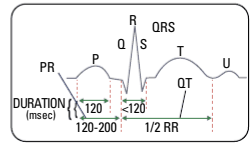

Figure 6. ECG waveforms and normal values

Indications for brief (12-lead ECG) or prolonged (24 h or more) monitoring

- myocardial injury, ischemia, or history of prior infarction
- conditions associated with palpitations or risk of serious arrhythmias (e.g. WPW, long QT, HCM, heart block, and bradycardia)
- conduction abnormalities (e.g. LBBB/RBBB)
- electrolyte abnormalities (e.g. hyperkalemia/hypokalemia)
- investigation of syncope, near syncope, or palpitations ("symptom/rhythm correlation")
- can be used for:
  - recording of cardiac rhythm during symptoms or antiarrhythmic drug monitoring
  - assessment of cardiac structure and function (e.g. RVH/LVH and cardiomyopathy)
  - detection of non-sustained arrhythmias that require prophylactic intervention

For more examples and practice visit www.ecgmadesimple.com

Approach to ECGs

Introduction

Below, we are presenting both the classical approach and the newer PQRSTU approach to provide students with different ways to view the ECG. Despite methodological differences, the rigor and final result is the same.

Classical Approach to ECGs

RATE

- normal = 60-100 bpm
- atrial rates above normal range:
  - 150-250 bpm = AVNRT, AVRT, AT, (sinus tachycardia)
  - 250-350 bpm = atrial flutter
  - >350 bpm = AFib (note: atrial "rate" is not discernible)
- regular rhythm (defined by equal R-R or P-P intervals between beats)
  - rate can be calculated using either of the following two methods:
    - divide 300 by the number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 s)
    - use the square counting method by counting the number of big boxes between the R waves using the following sequence of numbers: 300 (1 box)-150 (2 boxes)-100 (3 boxes)-75 (4 boxes)-60 (5 boxes)-50 (6 boxes)
- irregular rhythm
  - rate = 6 x number of R-R intervals in 10 s (a standard ECG is 10 s)
- atrial escape rhythm in case of sinus node failure = 60-80 bpm, junctional escape rhythm = 40-60 bpm, ventricular escape rhythm = 20-40 bpm

Classical Approach to ECG

Rate
Rhythm (defined by R-R or P-P intervals between beats)
Axis
Conduction abnormalities
Hypertrophy/chamber enlargement
Ischemia/infarction
Miscellaneous ECG changes (e.g. QT interval)

Differential Diagnosis for Left Axis Deviation

Normal variant (physiologic, often age-related change)
Left anterior hemiblock
LVH
Inferior MI
WPW
RV pacing
Elevated diaphragm
Lead misplacement
Congenital heart disease (e.g. primum ASD, endocardial cushion defect)
Hyperkalemia
Emphysema

RHYTHM

- regular: R-R interval is the same across the tracing
- irregular: R-R interval varies across the tracing
- regularly irregular: repeating pattern of varying R-R intervals (e.g. Wenckebach)
- irregularly irregular: R-R intervals vary erratically (e.g. AFib, atrial flutter with variable block, VFib)
- normal sinus rhythm (NSR)
  - P wave precedes each QRS; QRS follows each P wave
  - P wave axis is normal (positive in 2 of the following 3 leads: I, II, aVF)
  - rate between 60-100 bpm

AXIS

- mean axis indicates the direction of the mean vector
- can be determined for any waveform (P, QRS, T)
  - the standard ECG reported QRS axis usually refers to the mean axis of the frontal plane it indicates the mean direction of ventricular depolarization forces
- QRS axis in the frontal plane
  - normal axis: -30° to 90° (i.e. positive QRS in leads I and II)
  - left axis deviation (LAD): axis <-30°
  - right axis deviation (RAD): axis >90°
- QRS axis in the horizontal plane is not routinely calculated
  - transition from negative to positive is usually in lead V3

Table 1. Conduction Abnormalities

Left Bundle Branch Block (LBBB)	Right Bundle Branch Block (RBBB)
Complete LBBB QRS duration >120 msec Broad notched R waves in leads I, aVL, V5, and V6 Deep broad S waves in leads V1-2 Secondary ST-T changes (-ve in leads with broad notched R waves, +ve in V1-2) are usually present LBBB can mask ECG signs of MI LBBB: lead V1 negative, V6 positive and notched	**Complete RBBB** QRS duration >120 msec Positive QRS in lead V1 (rSR' or occasionally broad R wave) Broad S waves in leads I, V5-6 (>40 msec) Usually secondary T wave inversion in leads V1-2 Frontal axis determination using only the first 60 msec RBBB: V1 is positive (rSR'), V6 has broad S wave

Left Anterior Fascicular Block (LAFB) (Left Anterior Hemiblock)	Left Posterior Fascicular Block (LPFB) (Left Posterior Hemiblock)	Bifascicular Block
Left Axis Deviation (-30° to -90°) Small Q and prominent R in leads I and aVL Small R and prominent S in leads II, III, and aVF	**Right Axis Deviation (110° to 180°)** Small R and prominent S in leads I and aVL Small Q and prominent R in leads II, III, and aVF	**RBBB Pattern** Small Q and prominent R The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks

Nonspecific Intraventricular Block

- QRS duration >120 msec
- absence of definitive criteria for LBBB or RBBB

Table 2. Hypertrophy/Chamber Enlargement

Left Ventricular Hypertrophy	Right Ventricular Hypertrophy
S in V1 + R in V5 or V6 >35 mm above age 40, (>40 mm for age 31-40, >45 mm for age 21-30) R in aVL >11 mm R in I + S in III >25 mm Additional criteria LV strain pattern (asymmetric ST depression and T wave inversion in leads I, aVL, and V4-V6) Left atrial enlargement N.B. The greater the number of criteria, the more likely the diagnosis is LVH. If only one voltage criteria present, it is called minimal voltage criteria for LVH (may be a normal variant)	Right axis deviation R/S ratio >1 or qR in lead V1 RV strain pattern: ST segment depression and T wave inversion in leads V1-2
Left Atrial Enlargement	**Right Atrial Enlargement**
Biphasic P wave with the negative terminal component of the P wave in lead V1 ≥1 mm wide and ≥1 mm deep P wave >100 msec, could be notched in lead II ("P mitrale")	P wave >2.5 mm in height in leads II, III, or aVF ("P pulmonale")

Differential Diagnosis for Right Axis Deviation

- Normal variant (vertical heart with an axis of 90°)
- RVH
- Left posterior hemiblock
- Pulmonary embolism
- COPD
- Lateral MI
- WPW
- Dextrocardia
- Septal defects

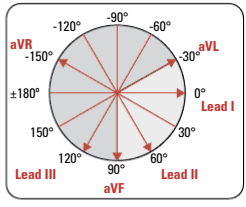

Figure 7. Axial reference system
Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead result in an upward deflection in that lead. Normal QRS axis is between -30° and +90°

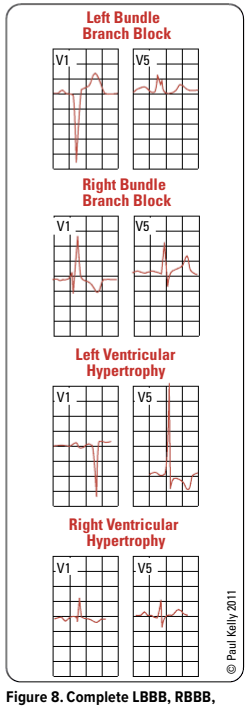

Figure 8. Complete LBBB, RBBB, LVH, and RVH (please see online examples for the full range of waveforms and the text for additional characteristics)

ISCHEMIA/INFARCTION

- look for the anatomic distribution of the following ECG abnormalities (see *Table 3*)
  - ischemia
    - ST segment depression
    - T wave inversion
  - injury/infarct
    - transmural (involving the entire wall thickness)
      - ST elevation in the leads facing the injured/infarcted area
    - subendocardial
      - marked ST depression in the leads facing the affected area
  - may be accompanied by enzyme changes (in infarction) and other signs of MI

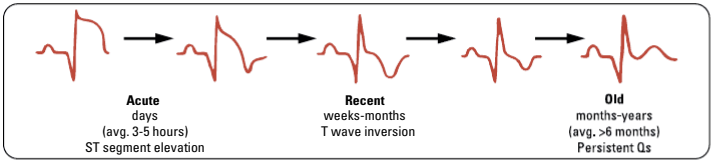

Figure 9. Typical ECG changes with infarction
Note that Q waves may gradually appear over time (not shown here)

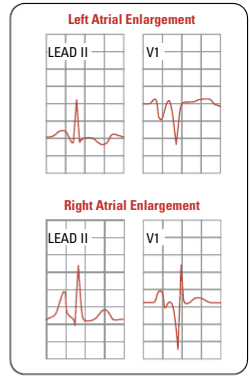

Figure 10. LAE, RAE (please see online examples and the text for characteristics)

  - ST elevation
    - new ST elevation in two contiguous leads of >0.1 mV (in all leads other than leads V2-V3)
    - for leads V2-V3: ≥0.2 mV in men ≥40 yr, ≥0.25 mV in men <40 yr, or ≥0.15 mV in women
- "typical" sequential changes of evolving MI
  1. hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
  2. ST elevation (injury pattern) in the leads facing the infarcted area
     - usually in the first hours post-infarct
     - in acute posterior MI, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads that are not recorded in the standard 12-lead ECG) hence get a 15-lead ECG
  3. significant Q waves: >40 msec or >1/3 of the total QRS amplitude and present in at least 2 consecutive leads in the same territory (hours to days post-infarct)
     - Q waves of infarction may appear in the very early stages, with or without ST changes
     - non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction
  4. inverted T waves (one day to weeks after infarction)
- completed infarction
  - abnormal Q waves (Q waves may be present in lead III in normal individuals due to initial septal depolarization)
  - duration >40 msec (>30 msec in aVF for inferior infarction)
  - Q wave is >1/3 of the total QRS amplitude
  - present in at least 2 consecutive leads in the same territory
  - abnormal R waves (R/S ratio >1, duration >40 msec) in V1, and occasionally in V2, are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)

Table 3. Areas of Infarction/Ischemia (right dominant anatomy)

Vessel Usually Involved	Infarct Area (LAD and LCx)	Leads (LAD and LCx)
LAD	Anteroseptal	V1, V2
	Anterior	V3, V4
	Anterolateral	I, aVL, V3-6
	Extensive anterior	I, aVL, V1-6
RCA	Inferior	II, III, aVF
	Right ventricle	V3R, V4R (right-sided chest leads)
	Posterior MI (associated with inferior MI)	V1, V2 (prominent R waves)
LCx	Lateral	I, aVL, V5-6
	Isolated posterior MI	V1, V2 (prominent R waves)

Pacemakers
- Atrial pacemaker has discharge ("spike") prior to P wave
- Ventricular pacemaker has a pacemaker spike prior to the QRS which is usually broader with a LBBB morphology

MISCELLANEOUS ECG CHANGES

Electrolyte Disturbances

- hyperkalemia
  - mild to moderate (K +5-7 mmol/L): tall, peaked T waves
  - severe (K +>7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show abnormal morphology, axis shifts left or right, ST shift with tall T waves, eventually becomes a "sine wave" pattern
- hypokalemia
  - ST segment depression, prolonged QT interval (with risk for Torsades de Pointes VT if extreme), low T waves, prominent U waves (U>T)
  - enhances the toxic effects of digitalis

- hypercalcemia
  - shortened QT interval (more extracellular Ca^{2+} means shorter plateau in cardiac action potential)
- hypocalcemia
  - prolonged QT interval (less extracellular Ca^{2+} means longer plateau in cardiac action potential)

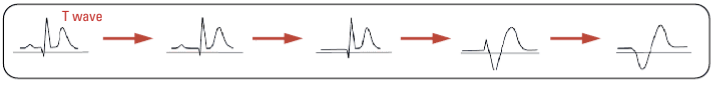

Figure 11. Hyperkalemia

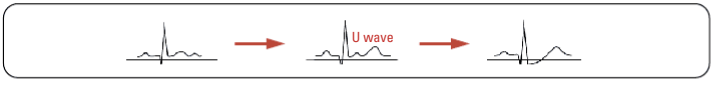

Figure 12. Hypokalemia

Hypothermia

- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- AFib with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves: "hump-like" waves at the junction of the J point and the ST segment

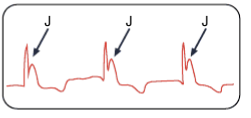

Figure 13. Osborne J waves of a hypothermic patient

Pericarditis

- early: diffuse ST segment elevation ± PR segment depression, upright T waves
- later: isoelectric ST segment, flat or inverted T waves
- ± tachycardia

Drug Effects

- digitalis (cardiac glycoside) poisoning rare in 2021; <1/1000 cardiac patients overall
  - therapeutic levels may be associated with "digitalis effect"
    - ST downsloping or "scooping"
    - T wave depression or inversion
    - QT shortening ± U waves
    - slowing of ventricular rate in AFib
    - most common rhythm disturbance: PVCs
  - toxic levels associated with:
    - arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradycardia in AFib, accelerated junctional rhythms, PVCs, VT (see *Arrhythmias, C19*)
    - "regularization" of ventricular rate in AFib due to complete heart block with junctional escape rhythm
- amiodarone, quinidine, phenothiazines, mood stabilizing medications (including tricyclic antidepressants and antipsychotics), some antihistamines, antifungals, and some antibiotics
  - prolonged QT interval, U waves

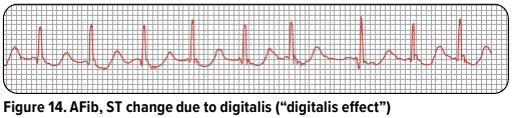

Figure 14. AFib, ST change due to digitalis ("digitalis effect")

Digitalis Side Effects
Palpitations, fatigue, visual changes (yellow vision), decreased appetite, hallucinations, confusion, and depression

Pulmonary Disorders

- cor pulmonale (often secondary to COPD)
  - low voltage, right axis deviation (RAD), poor R wave progression in precordial leads
  - RAE and RVH with strain
  - multifocal atrial tachycardia
- massive pulmonary embolism
  - sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  - RAD, RVH with strain
  - most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III) but rather uncommon

Alternative PQRSTU Approach to ECGs

Note: the PQRSTU Approach is organized a different way based on the anatomy of the ECG

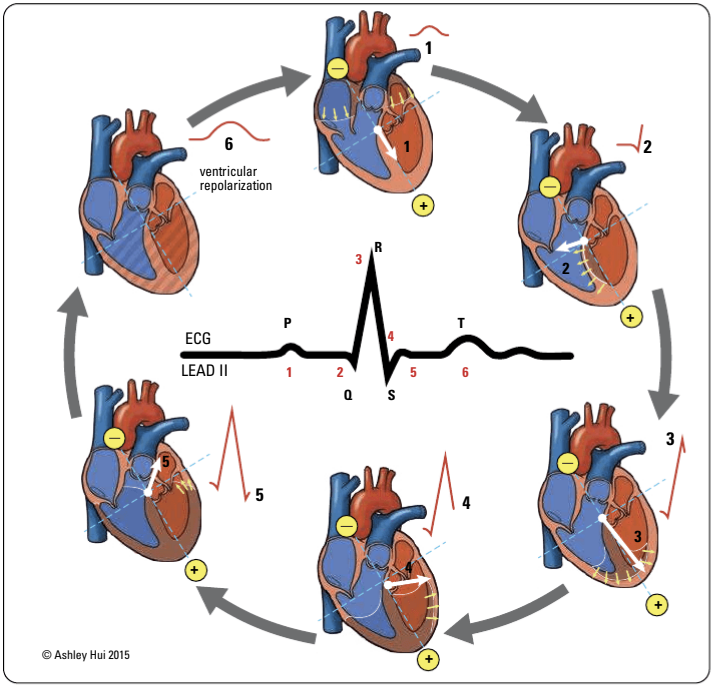

Figure 15. ECG correlations with heart activity

PQRSTU Approach to ECGs
P wave
P-R interval
QRS complex
ST segment
T wave
Q-T interval
U wave

P WAVE

- the P wave represents atrial contraction, best seen in leads: II and V1
  - lead II: the P wave should be rounded, <120 msec and <2.5 mm in height
  - lead V1: the P wave is biphasic with a positive phase, followed by a negative phase
- atrial flutter: "sawtooth" P wave with continuous atrial activity at 300 bpm indicates the interval (Hints: flip the ECG upside-down and check inferior leads (II, III, and aVF) to see it better)
- AFib: absent P wave, may have fibrillatory wave, irregularly irregular ventricular rhythm
- RAE: tall P wave (>2.5 mm) in II or V1 (P pulmonale)
- LAE: biphasic P wave with negative deflection >1 mm deep or >1 mm wide in V1, wide (>100 msec) notched P wave in II may be present (P mitrale)

P-R INTERVAL

- the P-R interval indicates the interval between sinus node activation and the start of ventricular depolarization
  - includes the impulse traveling through the atria, the AV node, and the bundle of His. The magnitude of the conduction velocity is referred to as "dromotropy" (faster = positive dromotropy, slower = negative dromotropy)
  - positive dromotropy associated with increased conduction velocity (e.g. sympathetic stimulation), while negative dromotropy is associated with decreased velocity (e.g. vagal stimulation)
- P-R interval should be 120-200 msec
- long P-R interval (>200 msec)
  - heart block (may be due to disease, delay in the AV node, or delay in distal (His-Purkinje) conduction system)
    - first degree: fixed, prolonged P-R interval (though every P wave has a QRS following)
    - second and third degree AV block: some P waves are NOT followed by a QRS
    - second degree Mobitz I (Wenckebach): gradual prolongation of the P-R interval precedes a dropped P wave
    - second degree Mobitz II (Hay): fixed P-R interval with ratio of atrial to dropped ventricular beats (e.g. for every 3 atrial beats, there is one ventricular beat (3:1))
    - third degree/complete: constant P-P and R-R intervals but variable P-R intervals

Significant ECG Changes

Look for ST changes starting at 60 msec from J point

J point = the junction between the QRS complex and the ST segment

ST elevation: at least 1 mm in 2 adjacent limb leads, or at least 1-2 mm in adjacent precordial leads

ST depression: downsloping or horizontal

Q Wave: pathological if Q wave ≥1 small square (≥40 msec) or >1/3 of the total QRS amplitude

- hypokalemia
- "trifascicular" block: long PR segment (first degree AV block) and bifascicular block

• short P-R interval (<120 msec)
- pre-excitation syndrome (delta wave: upsloping of the first part of the QRS complex) due to accessory pathways
- low atrial rhythm, P waves inverted in II, III, and aVF

QRS COMPLEX

• represents ventricular contraction
• rate: check if R-R interval matches the P-P interval
• amplitude: check for hypertrophy (see *Table 2, C8*)
• narrow QRS (<120 msec) means that the His-Purkinje system is being used
• wide QRS (>120 msec) means that the His-Purkinje system is being bypassed or is diseased
- BBB, VT, ventricular hypertrophy, cardiomyopathy, WPW, ectopic ventricular beat, hyperkalemia, or drugs (e.g. tricyclic antidepressants, antiarrhythmics)

• Q wave: the first downward deflection of the QRS complex
- significant Q wave (>40 msec or >1/3 of total QRS amplitude) indicates myocardial necrosis (new or old)

• R and S wave abnormalities typically show pathology in terms of BBB or intraventricular abnormalities

Insignificant Q Wave
- Septal depolarization by the left bundle
- Seen in leads I, II, III, aVL, V5, and V6
- <40 msec
- Q wave <1/3 of the total QRS amplitude

ST SEGMENT

• located between QRS complex and the beginning of T wave
- corresponds to the completion of ventricular depolarization

• normally at the same level as baseline (T-P segment)
• ST elevation: see *Infarction, C9*
• ST depression: ischemia
- ischemia that causes ST depression can result in myocardial damage (NSTEMI)
- lateral ST depression (leads I, aVL, V5, V6) may actually indicate a STEMI in the right heart
- ST depression may be nonspecific, or associated with remote MI or ischemia

T WAVE

• repolarization phase of ventricles (repolarization of the atria is obscured by the QRS complex)
• typically positive (except in aVR and V1) on ECG but normal isolated negative T waves may be present (especially in V1 and V2)
• T wave variation in consecutive leads may indicate pathology
- inversion: BBB, ischemia, hypertrophy, drugs (e.g. digitalis), pulmonary embolism (lead III as part of S1Q3T3 sign)
- elevation: infarction (STEMI, Prinzmetal, hyperacute), hyperkalemia (wider, peaked)
- flattened: hypokalemia, pericarditis, drugs (e.g. digitalis), pericardial effusion
  - flat T waves are nonspecific with no clinical significance (common)
- variations: T wave alternans; beat-to-beat variations due to PVC overlap (R on T phenomenon which may precipitate VT or VFib)

• appropriate T wave discordance: in BBB, T wave deflection should be opposite to that of the terminal QRS deflection (i.e. T wave negative if ends with R or R'; positive if ends with S)
- inappropriate T wave concordance suggests ischemia or infarction

Differential Diagnosis of ST Segment Changes

ST Elevation – I HELP A PAL
Ischemia with reciprocal changes
Hypothermia (Osborne waves)
Early repolarization (normal variant, need old ECGs to confirm)
LBBB
Post-MI
Acute STEMI
Prinzmetal's (Vasospastic) angina
Acute pericarditis (diffuse changes)
Left/right ventricular aneurysm

ST Depression – WAR SHIP
WPW syndrome
Acute NSTEMI
RBBB/LBBB
STEMI with reciprocal changes
Hypertrophy (LVH or RVH) with strain
Ischemia
Post-MI

Q-T INTERVAL

• duration of ventricular depolarization plus repolarization; often difficult to interpret
• corrected QT (QTc) corrects for the repolarization duration (since QT interval normally shortens with increased HR)
- QTc = QT ÷ √RR (Bazett's formula. NOTE: Bazett formula is inaccurate at rapid rates (e.g. >100/min))

• normal QTc is 360-450 msec for males and 360-460 msec for females
- increased (>450 msec for males and >460 msec for females): risk of Torsades de Pointes (lethal tachyarrhythmia; rare if <520 msec)
  - genetic long QT syndrome (often a channelopathy)
  - drugs: antiarrhythmics (classes I and III), antipsychotics (haloperidol, ziprasidone), antidepressants (citalopram), antibiotics (erythromycin, azithromycin)
  - electrolytes: low Ca^{2+}, low K^+, low Mg^{2+}
  - others: hypothyroidism, hypothermia, cardiomyopathy
- decreased (<360 msec): risk of VFib (very rare)
  - electrolytes: high Ca^{2+}
  - drugs: digoxin
  - others: hyperthyroidism

U WAVE

• origin unclear but may be repolarization of Purkinje fibres or delayed/prolonged repolarization of the myocardium
• more visible at slower heart rates
• deflection follows T wave with <25% of the amplitude
• variations from norm could indicate pathologic conditions
- prominent (>25% of T wave): electrolyte (low K^+), drugs (digoxin, antiarrhythmics)
- inverted (from T wave): ischemia, volume overload

Cardiac Biomarkers

- provide diagnostic and prognostic information in acute coronary syndromes and in HF

Table 4. Cardiac Enzymes

Enzyme	Peak	Duration Elevated	DDx of Elevation
Troponin I, Troponin T	12-24 h	Up to 2 wk	MI, CHF, AFib, acute PE, aortic dissection, myocarditis, pericarditis, endocarditis, cardiac defibrillation, myocardial damage, infiltrative cardiomyopathy, ischemic stroke, intracranial hemorrhage, acute hypotension, chronic renal insufficiency, sepsis, hypovolemia, acute respiratory distress syndrome, chronic hypertension, diabetes mellitus, hypothyroidism, rhabdomyolysis
Creatine Kinase-MB (CK-MB)	1 d	3 d	MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, chronic renal insufficiency

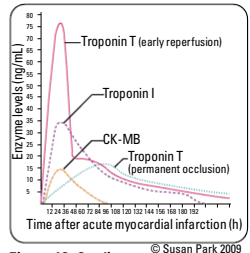

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Figure 16. Cardiac enzymes

- timing for troponin measurements is dependent on the assay used
  - high-sensitivity troponin I and T assays detect elevations in cardiac troponin earlier than traditional assays
- new CK-MB elevation can be used to diagnose re-infarction
- other biomarkers of cardiac disease
  - CK-MB, AST, and lactate dehydrogenase (LDH) also increases in MI (low specificity)
  - BNP and N-terminal prohormone of BNP (NT-proBNP): secreted by ventricles in response to increased end-diastolic pressure and volume
    - DDx of elevated BNP: CHF, AFib, PE, pulmonary HTN

Ambulatory ECG

- description
  - provides a view of two or three leads of electrocardiographic data over an extended period of time
  - permits evaluation of changing dynamic cardiac electrical phenomena
  - the choice of monitor depends on the patient's reported symptom frequency
    - if daily symptoms, use a 24 h or 48 h continuous ECG (Holter) monitor
    - if less frequent (i.e. weekly or monthly), use prolonged continuous monitoring (1-2 wk) or an event monitor
  - **continuous ambulatory monitor**: a small, lightweight, battery-operated recorder (box or patch) which records two or three channels of electrocardiographic data
    - patient activated event markers
    - minimum of 24-72 h, up to 14 d
  - **implantable loop recorder (ILR):** subcutaneous monitoring device for the detection of cardiac arrhythmias
    - typically implanted in the left pectoral region and stores events when the device is activated automatically according to programmed criteria or manually with magnet application
    - generally used for months to years
    - note: devices implanted for bradyarrhythmias (pacemakers) or tachyarrhythmias (defibrillators) also record rhythm continuously and have algorithms for automatic rhythm detection and storage
  - **external event monitor**
    - post-event monitoring device: placed on patient's chest after symptom onset and records "real-time" rhythm for a specified period (e.g. 30-150 s)
    - event/loop recorder: constantly records patient's rhythm for a period of time but only saves the data when the patient experiences symptoms and presses the event button (usually 30-60 s recall)
    - auto-triggered event recorder: uses programmed algorithms to auto-detect, capture, and save asymptomatic arrhythmias in addition to patient-triggered events
  - **patient administered single lead ECG**
    - wrist or finger electrodes, commercially available direct to consumer (e.g. Apple Watch, Kardia Mobile)
- **indications**
  - evaluation of cardiac rhythm abnormalities, especially as they correlate with symptoms and provoking factors
  - has also been used for assessing pacemaker and implantable cardioverter-defibrillator function, evidence of myocardial ischemia, late potentials, and HR variability

Echocardiography

Transthoracic Echocardiography

- **description**
  - non-invasive ultrasound directed across the chest wall to obtain real time images of the heart
- **indications**
  - evaluation of cardiac anatomy and functioning including: chamber size, wall thickness, wall motion, valve morphology, proximal great vessel morphology, and LVEF
  - evaluation of clinical cardiac abnormalities including: chest pain with hemodynamic instability, peripheral edema with elevated JVP, murmurs, unexplained hypotension, and syncope with suspected structural cardiac cause
  - evaluation of suspected cardiac diseases including: aortic dissection, congenital heart disease, LV thrombus, MI, pericardial effusion, and pericardial tamponade

Transesophageal Echocardiography

- **description**
  - ultrasound probe inserted into the esophagus to allow for better resolution of the heart and structures
  - better visualization of posterior structures, including LA, mitral, aortic valves, and inter-atrial septum
- **indications**
  - initial test in certain life-threatening situations (e.g. aortic dissection) when other tests contraindicated (e.g. CT angiography in patient with renal failure or when TTE is technically inadequate
  - key indication is to evaluate valvular morphology, vegetation (e.g. infective endocarditis), and function (e.g. stenosis and regurgitation) especially of the aortic, mitral, and prosthetic valves if present
  - evaluate cardiac disease including: aortic dissection, aortic atheromas, intracardiac thrombi, tumours, and shunts
  - evaluation for left atrial thrombus/left atrial appendage thrombus in a patient with AFib/atrial flutter to facilitate clinical decision making regarding electrical cardioversion or ablation
- **risks**
  - serious complications are extremely rare (<1 in 5000)
  - esophageal perforation
  - gastrointestinal bleeding
  - pharyngeal hematoma

Stress Echocardiography

- **description**
  - echocardiography using exercise (treadmill or bicycle) or pharmacologic agents (dobutamine or adenosine) as physiological stressor
- **indications**
  - when other stress imaging modalities are unequivocal or when ECG is non-diagnostic
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - post-ACS to decide on potential efficacy of revascularization (i.e. myocardial viability)
  - evaluate the clinical significance of valvular heart disease: AS, MS, MR, or AR
  - evaluation of cardiac disease: LV systolic dysfunction of unclear etiology, latent or established pulmonary HTN, LVOT obstruction in HCM, and syncope of unclear etiology
  - dobutamine
    - pharmacologic stress for patients physically unable to exercise; same indications as exercise stress echocardiogram
    - low dose dobutamine stress echocardiogram can be used to assess myocardial viability and to assess AS with LV systolic dysfunction
- **contraindications**
  - absolute contraindications to exercise testing (see below)
  - contraindications to dobutamine stress echocardiography: tachyarrhythmias and systemic hypertension
  - relative contraindications to both exercise and dobutamine stress echocardiography: AAA, electrolyte abnormalities, left main CAD, and moderate stenotic valvular disease

Contrast Echocardiography with Agitated Saline Contrast

- **description**
  - improves visualization and provides real-time assessment of intracardiac blood flow
  - conventional agent is agitated saline (contains microbubbles of air)
  - visualization of right heart and intracardiac shunts, most commonly PFO and intrapulmonary shunt
  - in a normal heart, microbubbles are still seen but only in the right heart and eventually diffuse into lungs after travelling through pulmonary circulation

- **indications**
  - detection of right-to-left shunts the presence of microbubbles in the left heart chambers indicates a right-to-left intracardiac or extracardiac shunt
  - Doppler signal enhancement agitated saline enhances tricuspid Doppler signals; this could be used to assess transvalvular velocity and to estimate right ventricular systolic pressure
  - diagnosis of persistent left superior vena cava if contrast injected in left arm vein appears in the coronary sinus before the RA

Contrast Echocardiography with Transpulmonary Contrast Agents

- **description**
  - newer contrast agents such as Definity® contrast can cross the pulmonary bed and achieve left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders, enhance evaluation of LVEF , wall motion abnormalities (in patients with technically inadequate echocardiograms), and intracardiac mass (e.g. LV thrombus)
- **risks**
  - major complications (e.g. risk of non-fatal MI and death are rare)
  - ultrasound contrast agents may cause back pain, headache, urticaria, and anaphylaxis
  - caution in patients with significant intra-cardiac shunts

Stress Testing

EXERCISE TESTING

- **description**
  - cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring for the detection of inducible myocardial ischemia, exercise related symptoms (e.g. arrhythmias), or objective measures of exercise tolerance
  - exercise test results stratify patients into 3 risk groups:
    1. low-risk: can treat medically without invasive testing
    2. intermediate-risk: may need additional testing in the form of exercise imaging studies or cardiac catheterization
    3. high-risk: refer for cardiac catheterization
- **indications**
  - patients with intermediate (10-90%) pretest probability of myocardial ischemia (usually due to CAD) based on age, gender, and symptoms
  - ST depression <1 mm at rest, LBBB, digoxin or estrogen use make the ST changes difficult to interpret however, graded exercise stress test can still be valuable
  - important prognostic and diagnostic information (beyond ST changes) is obtained from symptoms, total exercise time, HR, and BP response to exercise, if arrhythmia is provoked
    - note: this is a diagnostic test with false positives and false negatives. Management needs to take into account symptoms and exercise tolerance
- **absolute contraindications**
  - acute MI (within 2 d) or unstable angina pectoris
  - uncontrolled arrhythmias causing symptoms of hemodynamic compromise
  - symptomatic severe valvular stenosis
  - uncontrolled symptomatic HF
  - active endocarditis, acute myocarditis, or pericarditis
  - acute aortic dissection
  - acute pulmonary or systemic embolism
  - acute non-cardiac disorders that may affect exercise performance or may be aggravated by exercise
  - termination of exercise testing
    - target HR achieved
    - patient's desire to stop
    - drop in sBP of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
    - moderate to severe angina
    - ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
    - increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
    - signs of poor perfusion (cyanosis or pallor)
    - technical difficulties in monitoring ECG or sBP
    - sustained VT
- **risks**
  - death, MI, arrhythmia, hemodynamic instability, and orthopedic injury (<1-5/10000 supervised tests)

Most Commonly Used Treadmill Stress Test Protocols

The Bruce Protocol: 7 stage test with each stage lasting 3 min. With each successive stage, the treadmill increases in both speed (2.7 km/h to 9.6 km/h) and grade (10% with a 2% increase per stage up to 22%)

The Modified Bruce, Modified Naughton Protocol: for older individuals or those with limited exercise capacity

Important Contraindications to Exercise Testing

- Acute MI, aortic dissection, pericarditis, myocarditis, PE
- Severe AS, arterial HTN
- Inability to exercise adequately

Important Prognostic Factor
Duke Treadmill Score (DTS)
Weighted Index Score

Treadmill exercise time using standard Bruce protocol
Maximum net ST segment deviation (depression or elevation)
Exercise-induced angina provides diagnostic and prognostic information (such as 1 yr mortality)

DTS = exercise time – (5 x MaxST) – (4 x angina index)
Angina index: 0 (no angina), 1 (angina but not exercise-limiting), 2 (exercise-limiting angina)
DTS ≥5: 0.25% 1 yr mortality
DTS 4 to -10: 1.25% 1 yr mortality
DTS ≤ -11: 5.25% 1 yr mortality
Ann Intern Med 1987;106:793-800

Patients with normal imaging (nuclear perfusion or stress echo) studies at peak stress have a <1%/yr incidence of death or nonfatal MI and are thus often spared further invasive evaluation

NUCLEAR CARDIOLOGY

- **description**
  - MPI with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
  - evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously
  - predicts the likelihood of future cardiac event rates independent of the patient's history, examination, resting ECG, and stress ECG
  - often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi)
  - stress with either treadmill or IV vasodilator stress (e.g. dipyridamole, adenosine, regadenoson)
  - images of the heart obtained during stress and at rest 3-4 h later
  - tracers
    - Thallium-201 (^{201}Tl, a K^+ analogue)
    - Technetium-99 (^{99}Tc)-labeled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®)
- **indications**
  - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarker
  - exercise MPI
    - when ECG cannot be interpreted appropriately due to LBBB or abnormal baseline ECG
    - intermediate pre-test probability with normal/equivocal exercise ECG
    - in patients with previous imaging whose symptoms have changed
    - to diagnose ischemia
  - dipyridamole/adenosine MPI
    - exercise testing is always preferred
    - pharmacological stress imaging test for patients who cannot exercise or do not want to hold cardiac medications (β-blockers/CCBs)
    - same indication as exercise MPI
- **contraindications**
  - vasodilators (i.e. adenosine, regadenoson, and dipyridamole) are contraindicated in patients with hypotension, sick sinus syndrome, high-degree AV block (in the absence of backup pacemaker capability), and reactive airways disease
  - pregnancy
- **risks**
  - radiation exposure

STRESS ECHOCARDIOGRAPHY

- see *Echocardiography, C14*

Cardiac Catheterization and Angiography

Right Heart Catheterization (Swan-Ganz Catheter)

- **description**
  - also known as pulmonary artery catheterization
  - obtain direct measurements of central venous, right-sided intracardiac, pulmonary artery, and pulmonary artery occlusion pressures
  - can estimate CO, SVR, and PVR as well as mixed venous oxyhemoglobin saturation, oxygen delivery, and oxygen uptake
  - right atrial, right ventricular, and pulmonary artery pressures are recorded
  - can also be used to measure the Cardiac Index (CI), a measure of cardiac function
    - CI = CO/body surface area
    - 2.6-4.2 L/min/m ^{2} is considered normal while <1.8 L/min/m ^{2} usually means cardiogenic shock
  - PCWP
    - obtained by advancing the catheter to wedge in the distal pulmonary artery
    - records pressure measured from the pulmonary venous system
    - in the absence of pulmonary venous disease, reflects left atrial pressure
- **indications**
  - unexplained or unknown volume status in shock
  - severe cardiogenic shock (e.g. acute valvular disease, suspected pericardial tamponade)
  - suspected or known pulmonary artery HTN
  - severe underlying cardiopulmonary disease (e.g. congenital heart disease, left-to-right shunt, severe valvular disease, pulmonary HTN) and undergoing surgery (e.g. corrective)
- **contraindications**
  - infection at the insertion site
  - presence of a right VAD
  - insertion during cardiopulmonary bypass

- **risks**
  - complications for diagnostic catheterization: <1%
  - inadequate diagnostic procedures occur in <1% of cases
  - complications of insertion: atrial and/or ventricular arrhythmias (~3% of patients)
  - catheter misplacement or knotting (uncommon)
  - perforation of a cardiac chamber and rupture of a cardiac valve or the pulmonary artery (rare)
  - complications of catheterization: pulmonary artery rupture, pulmonary infarction, thromboembolic events, infection, and data misinterpretation
  - within 24 h of catheterization: death, MI, or stroke (0.2% to 0.3% of patients)

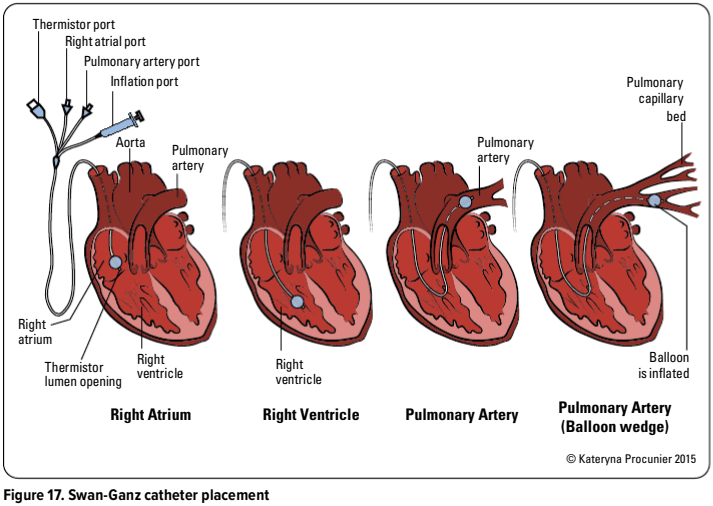


Figure 17. Swan-Ganz catheter placement

Left Heart Catheterization

- **description**
  - accomplished by introducing a catheter into the radial, brachial, or femoral artery and advancing it through the aorta, across the aortic valve, and into the LV
  - evaluates mitral and aortic valvular defects and myocardial disease
  - systolic and end-diastolic pressure tracings recorded
  - LV size, wall motion, and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
- **indications**
  - identification of the extent and severity of CAD and evaluation of left ventricular function
  - assessment of the severity of valvular or myocardial disorders (e.g. AS or insufficiency, MS or insufficiency, and various cardiomyopathies) to determine the need for surgical correction
  - collection of data to confirm and complement non-invasive studies
  - investigating CAD in patients with confusing clinical features or chest pain of uncertain origin
- **contraindications**
  - severe uncontrolled HTN
  - ventricular arrhythmias
  - acute stroke
  - severe anemia
  - active gastrointestinal bleeding
  - allergy to radiographic contrast
  - acute renal failure
  - uncompensated congestive failure (patient cannot lie flat)
  - unexplained febrile illness or untreated active infection
  - electrolyte abnormalities (e.g. hyperkalemia)
  - severe coagulopathy
- **risks**
  - major complications of diagnostic catheterization (i.e. death, MI, stroke): <3 in 1000
  - minor complications (e.g. vascular access issue, kidney dysfunction): <1 in 100
  - inadequate diagnostic procedures occur in <1% of cases

Chambers	Pressure (systolic; mmHg)
Right atrium/central venous	1-8
Right ventricle	1-8 (15-30)
Pulmonary artery	4-12 (15-30)
Left atrium/pulmonary capillary wedge	4-12
Left ventricle end diastolic	4-12

Coronary Angiography

- **description**
  - radiographic visualization of the coronary vessels after injection of radiopaque contrast media
  - coronary vasculature accessed via the coronary ostia
- **indications**
  - to define the coronary anatomy and the degree of luminal obstruction of the coronary arteries
  - to determine the presence and extent of obstructive CAD
  - to assess the feasibility and appropriateness of various forms of therapy, such as revascularization by percutaneous or surgical interventions
  - can be used when the diagnosis of CAD is uncertain and cannot be excluded by non-invasive techniques
- **contraindications**
  - severe renal failure due to contrast agent toxicity (must check patient's renal status)
- **risks**
  - major complications of diagnostic catheterization (i.e. death, MI, stroke): <3 in 1000
  - minor complications (e.g. vascular access issue, kidney damage): <1 in 100

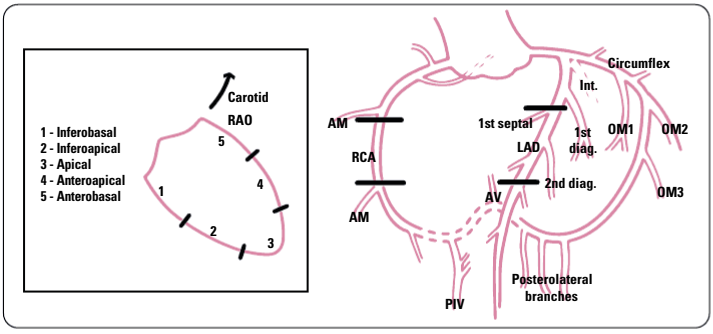


Figure 18. Coronary angiogram schematic
AM = acute marginal; LAD = left anterior descending; OM = obtuse marginal; RAO = right anterior oblique; RCA = right coronary artery

Diagnostic Catheterization

- provocative pharmacological agents can be used to unmask pathology
  - fluid loading may unmask latent pericardial constriction
  - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in HCM
  - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  - a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, CCBs, adenosine, nitric oxide, prostacyclin)

Contrast-Enhanced CT Coronary Angiography

- **description**: fast ECG-synchronized multi-slice CT image acquisition in the heart to enable non-invasive imaging of the coronary arterial tree
- **indications**: often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
- sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis
- **contraindications**: allergy to contrast dye; severe renal dysfunction; irregular heart rhythm or tachycardia which may impact image quality
- **risks**: radiation exposure; and contrast induced nephropathy

Magnetic Resonance Imaging

- **description**
  - offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
  - often used with gadolinium injection to assess myocardial scar
- **indications**
  - valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, assessment of viable myocardium, and assessment of cardiomyopathies
    - most accurate measure of ejection fraction
    - especially valuable for assessing RV

ACC/AHA 2011 Recommended Indications for Coronary Angiography
- Disabling chronic stable angina (CCS classes II and IV) despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Serious ventricular arrhythmia or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing

Coronary Angiography
Gold standard for localizing and quantifying CAD

Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter

- **contraindications**
  - metallic foreign bodies/implants (e.g. pacemaker, ICD, CRT, cerebral aneurysm clips, metal shrapnel, piercings)
  - kidney dysfunction due to gadolinium contrast medium
- **risks**
  - hazards posed by certain metallic devices inside patients

CARDIAC DISEASE

Arrhythmias

Mechanisms of Arrhythmias

Alterations in Impulse Formation

A. Normal Automaticity

- impulses from the SA node, caused by spontaneous depolarization, result in the basic cardiac pacemaker function. "Downstream" cells in the AV node and Purkinje fibres also depolarize spontaneously, but at a slower rate; they serve as the "backup" pacemaking cells if the upstream rate is slower than the more distal spontaneous rate
- normal automaticity is influenced by:
  - neurohormonal tone (sympathetic tone increases and parasympathetic tone decreases spontaneous firing rate and thus HR)
  - myocardial ischemia/infarction or other cardiac pathology (e.g. HF) may alter HR via these mechanisms
  - abnormal metabolic conditions (e.g. hypoxia, acidosis, hypothermia)
  - electrolyte abnormalities, especially hyperkalemia which slows HR
  - drugs (e.g. digitalis, β-blockers, CCB)
  - athletic training: endurance athletes often have sinus bradycardia
  - age: elderly often have sinus bradycardia
  - increased circulatory demand can result in sinus tachycardia (e.g. pregnancy, anemia, exercise)

Sinus Arrhythmia

- Normal P waves, with variation of the P-P interval, especially with respiration, due to varying rate of SA node depolarization

Respiratory SA

- Seen more often in young adults
- Normal, physiologic results from changes in autonomic tone during respiratory cycle
- Rate increases with inspiration, slows with expiration

Non-Respiratory SA

- Seen more often in the elderly
- Can occur in the normal heart; if marked may be due to sinus node dysfunction (e.g. in heart disease or after digitalis toxicity)
- Usually does not require treatment

B. Abnormal Automaticity due to Triggered Activity (due to Afterdepolarizations)

1. Early Afterdepolarizations

- during the terminal plateau or repolarization phases of action potential
- consequence of the membrane potential transiently becoming more positive during repolarization (depolarization interrupting repolarization)
  - these are called EADs and DADs (early and delayed afterdepolarization, respectively)
- may result in self-maintaining oscillations of depolarization, giving rise to action potentials thereby generating a tachyarrhythmia (e.g. new baseline voltage is greater than threshold, which automatically triggers a new action potential after the refractory period ends)
- EADs are the basis for the arrhythmias associated with QT prolongation, either congenital or acquired; termed "Torsades de Pointes"

2. Delayed Afterdepolarizations

- occur after the action potential has fully repolarized, but before the next usual action potential
- commonly occurs in situations of high intracellular calcium (e.g. digitalis intoxication, ischemia) or during enhanced catecholamine stimulation (e.g. "twitchy" pacemaker cells)

Alterations in Impulse Conduction

A. Re-Entry Circuits

- the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium (see *Figure 29, C24*, for an example in the context of AV nodal re-entrant tachycardia)
- the conditions necessary for re-entry include block of an impulse into a region of the heart that is refractory (non-excitable tissue or because of local functional block, where the impulse encounters tissue still in its refractory period), followed by "re-entry" of the impulse around a region of block to the site of origin, forming a complete re-entry circuit
  - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits
  - most sustained tachyarrhythmias are due to re-entry

B. Conduction Block

- ischemia, fibrosis, trauma, and drugs can cause transient or permanent, unidirectional or bidirectional block
- most common cause of block is "functional block" due to refractory myocardium (cardiomyocytes are in refractory period) or "anatomical block" (area of myocardium unexcitable due to fibrosis); cells in the conduction system distal to the block can assume pacemaking control if the block occurs along the specialized conduction system
- the consequence of conduction block are re-entry arrhythmias (tachyarrhythmias - see above) or failure of impulses to conduct to ventricular cells (bradycardia)
- conduction block in the AV node or His Purkinje tissue can lead to bradycardia

C. Bypass Tracts

- normally, the only electrical connection between atria and ventricles is the AV node and connected penetrating Bundle of His;
- an accessory bypass tract is a direct connection between A and V, histologically similar to atrial tissue, through the valve ring which is normally impenetrable to electrical impulses (hence "accessory atrio-ventricular bypass tract")
  - see *Pre-Excitation Syndromes, C25*

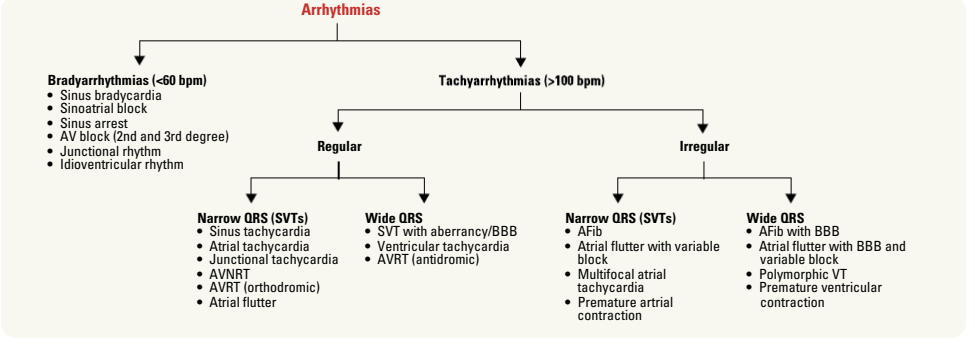


Figure 19. Clinical approach to arrhythmias

Bradyarrhythmias

Table 5. Types of Bradyarrhythmias

1. SA NODAL DYSFUNCTION

- P axis normal (P waves positive in I and aVF)
- Rate <60 bpm; marked sinus bradycardia (<50 bpm)
- May be seen in normal adults, particularly athletes, and in elderly individuals
- Increased vagal tone or vagal stimulation
- Drugs (e.g. β-blockers, CCB)
- Ischemia/infarction

Atropine; pacing for sick sinus syndrome

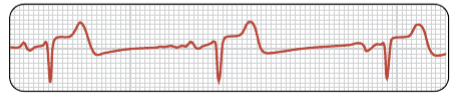


Figure 20. Sinus bradycardia

2. AV CONDUCTION BLOCKS

A. First Degree AV Block

- Prolonged PR interval (>220 msec)
- Frequently found among otherwise healthy adults

No treatment required

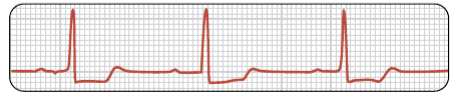


Figure 21. First degree AV block

B. Second Degree AV Block: Type I (Mobitz I)

- Gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
- AV block is usually in AV node (proximal) triggers (usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia

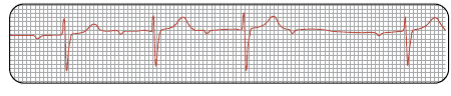


Figure 22. Second degree AV block with Wenckebach phenomenon (Mobitz I) (4:3 conduction) (lead V1)

Table 5. Types of Bradyarrhythmias

C. Second Degree AV Block: Type II (Mobitz II)

- The PR interval is constant; there is an abrupt failure of conduction of a P wave
- Often associated with distal conduction system disease (BBB)
- AV block is usually distal to the AV node (i.e. bundle of His); increased risk of high grade or third degree AV block

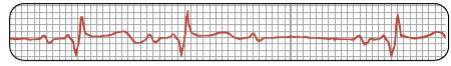


Figure 23. Second degree AV block (Mobitz II) (3:2 conduction) (lead V1)

D. Third Degree AV Block

- Complete failure of conduction of the supraventricular impulses to the ventricles
- Ventricular depolarization initiated by an escape pacemaker distal to the block
- Wide or narrow QRS, P-P and R-R intervals are constant, variable PR intervals
- No relationship between P waves and QRS complexes (P waves "marching through")

Management (see *Electrical Pacing, C29*)

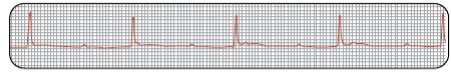


Figure 24. Third degree AV block (complete heart block) (lead II)

Supraventricular Tachyarrhythmias

Presentation for SVT (and Pre-Excitation Syndromes)

- presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate CHF, hypotension, or ischemia in patients with underlying cardiovascular disease
- untreated tachycardias of long duration (i.e. days) can cause tachycardia- induced cardiomyopathy (rare, potentially reversible with treatment of SVTs)
- arrhythmias involving the AV node (i.e. AVNRT and AVRT) may terminate spontaneously, after vagal stimulation, or after adenosine treatment

Supraventricular Tachyarrhythmias

- tachyarrhythmias that originate in the atria or involve the AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS unless there is pre-existing BBB or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

1. Sinus Tachycardia

- sinus rhythm with rate >100 bpm
- causes:
  - anxiety, exercise
  - metabolic (e.g. thyrotoxicosis, pheochromocytoma)
  - systemic demand (e.g. pregnancy, anemia, exercise, pain, fever, hypotension, hypovolemia, anemia, CHF, MI, shock, PE)
  - pharmacologic (e.g. cocaine, caffeine, alcohol, β-adrenergic agonists, anticholinergic drugs)
  - idiopathic (i.e. IST–idiopathic/inappropriate sinus tachycardia) or POTS (postural orthostatic tachycardia syndrome)
- treatment:
  - treat underlying disease; consider β-blocker if symptomatic, CCB if β-blockers contraindicated; ivabradine may be considered as an alternative agent for inappropriate sinus tachycardia

2. Premature Beats

- premature atrial contraction
  - ectopic supraventricular beat originating in the atria
  - P wave morphology of the PAC usually differs from that of a normal sinus beat
- junctional premature beat
  - ectopic supraventricular beat that originates in the vicinity of the AV node
  - P wave is usually absent or inverted, which may come before or closely follow the QRS complex (referred to as a retrograde, or "traveling backward" P wave)
- treatment usually not required

3. Atrial Flutter

- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly RA involving isthmus of tissue between tricuspid annulus and inferior vena cava (IVC))
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (e.g. 2:1, 3:1, 4:1, etc.) or variable
- etiology: HTN, cardiomyopathy, in association with AFib, age
  - less often: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis, in association with long term endurance sport/exercise
- ECG: "sawtooth" flutter waves (most common type of flutter, called "isthmus-dependent, typical flutter") in inferior leads, II, III, aVF; narrow QRS (unless aberrancy); commonly seen as 2:1 block with HR of 150
- in atrial flutter with 2:1 block, carotid sinus massage (after checking for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and allow flutter waves to be more easily seen

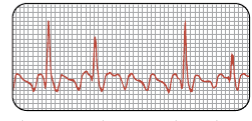


Figure 25. Atrial flutter with variable block

- treatment of acute atrial flutter
  - if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable:
    1. rate control: β-blocker, diltiazem, verapamil, or digoxin
    2. chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
    3. anticoagulation guidelines same as for patients with AFib
- long-term treatment of atrial flutter to prevent recurrences includes antiarrhythmics and radiofrequency (RF) ablation (for isthmus dependent, typical flutter, treatment of choice is RF ablation)

4. Multifocal Atrial Tachycardia (MAT)

- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
- atrial rate 100-200 bpm
  - 3 or more distinct P wave morphologies
  - PR intervals vary
  - some P waves may not be conducted
- more common in patients with COPD or hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline use, or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil); β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics, or ablation

5. Atrial Fibrillation

- see CCS Atrial Fibrillation Guidelines 2020 for details (free mobile app iCCS available on iOS and Android)
- the most common sustained arrhythmia
- risk factors: older age, hypertension, heart failure, valvular disease (especially leading to dilated LA), recent cardiac surgery, lung disease, excessive alcohol consumption, sepsis (particularly pneumonia)
- symptoms: palpitations, exercise intolerance, fatigue, dyspnea, dizziness, syncope, may precipitate or worsen HF. May also be completely asymptomatic
- **classification**
  - "lone": generally occurs in persons <65 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease (usually MS), or prosthetic heart valves, or valve repair
    - valvular disease is observed in patients/people with MS, prosthetic heart valves, or those who have undergone valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: AFib sustained for more than 7 d or AFib that terminates only with cardioversion
  - permanent/chronic: continuous AFib that is unresponsive to cardioversion or in which clinical judgement has led to a decision not to pursue cardioversion
  - recurrent: two or more episodes of AFib
  - secondary: caused by a separate underlying condition or event (e.g. MI, cardiac surgery, pulmonary disease, hyperthyroidism)
- **initiation**
  - single circuit re-entry and/or ectopic foci, mostly arising from the pulmonary veins, act as aberrant generators producing atrial tachycardia (350-600 bpm)
    - this leads to multiple re-entry circuitry (microre-entry)
  - impulses are conducted irregularly across the atrial myocardium to give rise to fibrillation
  - in most cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated
- maintenance
  - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AFib; the longer the patient is in AFib, the more difficult it is to restore normal sinus rhythm
- **consequences**
  - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response (usually <200 bpm); tachycardia leads to suboptimal CO
    - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation
      - AFib is an important risk factor for stroke or thromboembolic events (stroke risk can be assessed by CHADS2 score in AFib; CHADS2-VASc if the former gives a score of 0 or 1)
      - all valvular Afib (those with mechanical valves or MS) need anticoagulation but CHADS determines treatment for AS and MR

Table 6. CHADS2 Risk Prediction for Non-Valvular AFib

Risk Factor	Points	CHADS2 Score	Stroke Risk (%/Yr)
Congestive HF	1	0	1.9 (low)
HTN	1	1	2.8 (low-mod)
Age >75	1	2-3	4.0-5.9 (mod), need anticoagulation
Diabetes	1	4-6	8.5-18.2 (high), need anticoagulation
Stroke/TIA (prior)	2		

Can J Cardiol 2014;30:1114-30

- ECG findings
  - no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline

- irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
- wide QRS complexes due to aberrancy may occur following a long-short cycle sequence ("Ashman phenomenon")
- loss of atrial contraction, thus no "A" wave seen in JVP, no S4 on auscultation

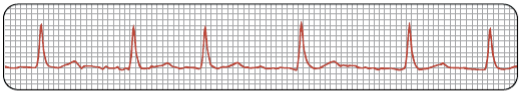


Figure 26. AFib (lead II)

- management (adapted from CCS Atrial Fibrillation Guidelines 2020)
  - primary goal is symptom control
  - stroke prevention is crucial, since patients who are not anticoagulated for AFib have, on average, a 4-5% annual stroke risk
  - all patients should be assessed for stroke risk and receive anticoagulation independent of the rate or rhythm treatment
  - **newly discovered AFib**
    - if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
    - if AFib persists, consider one of the following:
      1. rate control and anticoagulation (as indicated below)
      2. cardioversion (as indicated below)
    - an initial rhythm control strategy for patients with newly diagnosed AFib (i.e. within past year), is associated with reduced cardiovascular death and stroke rate
  - **recurrent or permanent AFib**
    - if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
    - patients who have undergone at least one attempt to restore sinus rhythm may remain in AFib after recurrence; permanent AFib may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations
    - if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
  - **drug selection for rhythm control**
    - no or minimal heart disease: flecainide, propafenone once proven to have no underlying CAD (may consider exercise stress testing)
    - LV dysfunction: amiodarone
    - CAD: β-blockers, amiodarone
    - if antiarrhythmic drugs fail or are not tolerated, can consider RF ablation for rhythm/symptom control
  - **treatment of AFib (RACE):** all patients with AFib (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk and risk of bleeding, and patients should receive an oral anticoagulant (OAC) if indicated
    1. **R**ate control: β-blockers, diltiazem, verapamil (in patients with HF: digoxin, amiodarone)
       - digoxin can be used to achieve rate control in patients whose response to β-blockers and/or CCB is inadequate, contraindicated, or not tolerated
    2. **A**nticoagulation: use either warfarin or DOACs (e.g. apixaban, dabigatran, rivaroxaban, edoxaban) to prevent thromboembolism
       - DOAC use is preferred to warfarin
       - for patients with non-valvular AFib (NVAF), OAC use is recommended for those >65 yr and/or with a CHADS2 ≥1. NVAF is defined as AF *not* due to mechanical valve or moderate-severe mitral stenosis
       - ASA 81 mg is recommended only for patients with none of the risks outlined in the CCS algorithm (age <65 and no CHADS2 risk factors) who also have arterial disease (coronary, aortic, or peripheral)
    3. **C**ardioversion (electrical)
       - if AFib <48 h, can usually cardiovert without anticoagulation (<12 h if high stroke risk)
       - if AFib >48 h, anticoagulate 3 wk before and 4 wk after cardioversion due to risk of unstable intra-atrial thrombus
       - if patient is unstable (hypotensive, active angina due to tachycardia, uncontrolled HF), cardiovert immediately
    4. **E**tiology
       - HTN, obesity, sleep apnea, CAD, heart failure, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, postoperative, PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol ("holiday heart")
       - may present in young patients without demonstrable disease ("lone AFib") and in the elderly without underlying heart disease
       - studies of patients with AFib suggest that there is no difference in long-term survival when treating patients with a rhythm-control vs. rate-control strategy (recent large study suggests benefit of rhythm control for recent onset AF- see above)
       - many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate AFib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible

The 2020 Canadian Cardiovascular Society/ Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation
Can J Cardiol 2020;36:1847-1948
Rate and Rhythm Control: Long-term rate control therapy in AFib patients is recommended to reduce symptoms and prevent CV events. Based on the paucity of data informing HR targets, it is recommended to titrate rate-controlling agents to achieve a resting HR <100 bpm during AFib. Rhythm control with long-term antiarrhythmic drug therapy might not completely suppress AFib, and thus should be focused on symptom relief, improving functional capacity, and reducing healthcare utilization. Rhythm control strategies are recommended for patients with established AFib who remain symptomatic with rate control therapy, or in whom rate control therapy is unlikely to control symptoms. In patients with newly diagnosed AFib, an initial strategy of rhythm control has been associated with reduced CV death and reduced incidence of stroke. It is recommended to consider catheter ablation of AFib as a reasonable alternative to pharmacologic rate or rhythm control.
Antithrombotic Therapy in AFib: In patients with AFib and coronary or arterial vascular disease, the choice of antithrombotic therapy should be based on a balanced risk assessment of AFib-related stroke, ischemic coronary events, and clinically relevant bleeding. If an oral anticoagulant is indicated, non-Vitamin K antagonist oral anticoagulants (NOACs) are recommended over warfarin.

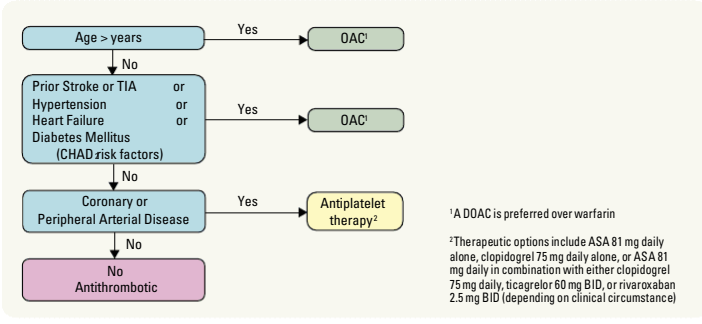

Age > years
Yes
OAC[1]
No
Prior Stroke or TIA or
Hypertension or
Heart Failure or
Diabetes Mellitus
(CHADS risk factors)
Yes
OAC[1]
No
Coronary or
Peripheral Arterial Disease
Yes
Antiplatelet therapy[2]
No
No Antithrombotic
[1]A DOAC is preferred over warfarin
[2]Therapeutic options include ASA 81 mg daily alone, clopidogrel 75 mg daily alone, or ASA 81 mg daily in combination with either clopidogrel 75 mg daily, ticagrelor 60 mg BID, or rivaroxaban 2.5 mg BID (depending on clinical circumstance)

Figure 27. CHADS-65: CCS algorithm for oral anticoagulation therapy in AFib

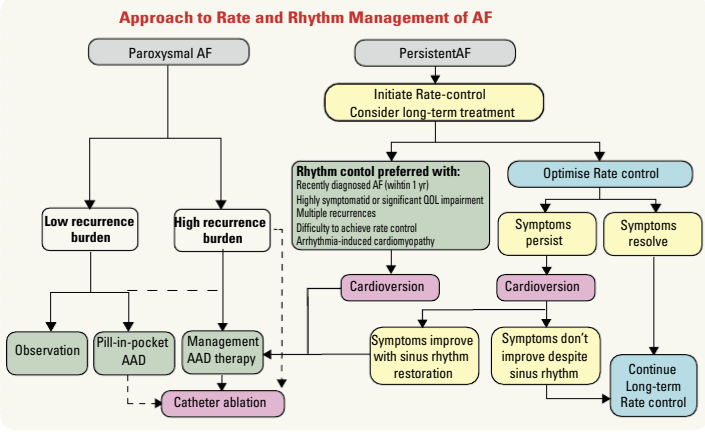


Figure 28. Approach to management of AFib

- **surgical management in AFib ablation**
  - sutured lesion
    - Cox-maze III: definitive surgical treatment of chronic AFib; indicated in patients who have failed maximal medical therapy and have had embolic events or are symptomatically compromised by AFib; 90-95% postoperative freedom from AFib; less likely to be successful in patients with large left atria (>5 cm) or with longstanding AFib (>5 yr)
    - modified maze and pulmonary vein isolation: more limited patient sets but takes less time to perform than classical maze procedure; selected cases can be done off bypass with concomitant OPCAB; 60-75% postoperative freedom from AFib
  - energy lesion
    - cryoablation: see *Catheter Ablation, C29*
    - radiofrequency ablation: see *Catheter Ablation, C29*
    - current experimental trials include use of laser ablation, microwave ablation, and ultrasound ablation

6. AV Nodal Re-Entrant Tachycardia

- re-entrant circuit using dual pathways (fast conducting β-fibres and slow conducting α-fibres) within or near the AV node; often found in the absence of structural heart disease
  - cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset with patients often describing "neck pounding" and "shirt flapping"
- fast regular rhythm of 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex
- treatment
  - acute: Valsalva maneuver or carotid sinus pressure technique, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina, or CHF)
  - long-term: 1st line radiofrequency ablation (>98% cure rate and < < 1% complication rate), β-blocker, diltiazem, digoxin; 2nd line flecainide, propafenone

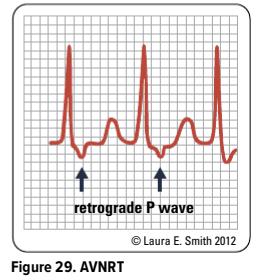


Figure 29. AVNRT

N.B. Refer to ECG Made Simple for further discussion and an animation of the mechanism(www.ecgmadesimple.com)

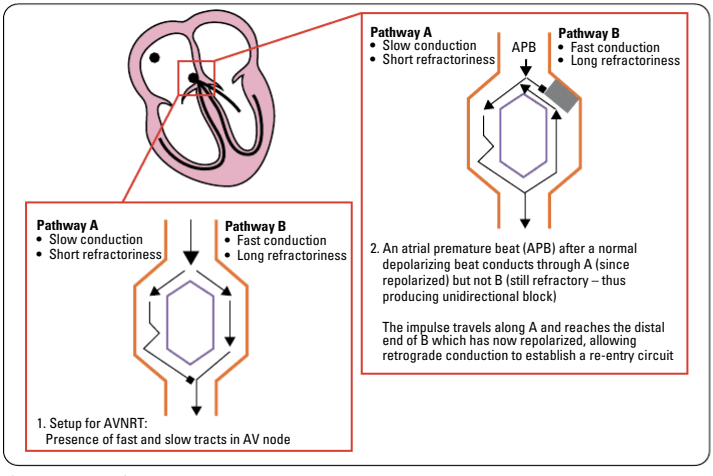

Pathway A
• Slow conduction
• Short refractoriness
Pathway B
• Fast conduction
• Long refractoriness
1. Setup for AVNRT:
Presence of fast and slow tracts in AV node
Pathway A
• Slow conduction
• Short refractoriness
APB
Pathway B
• Fast conduction
• Long refractoriness
2. An atrial premature beat (APB) after a normal depolarizing beat conducts through A (since repolarized) but not B (still refractory – thus producing unidirectional block)
The impulse travels along A and reaches the distal end of B which has now repolarized, allowing retrograde conduction to establish a re-entry circuit

Figure 30. Mechanism for AVNRT

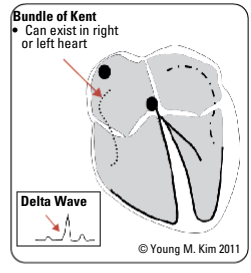


Figure 31. Accessory pathway conduction in WPW. Early ventricular activation leads to the appearance of a delta wave (slurred upstroke of the QRS) on the ECG before usual conduction across the AV node

Pre-Excitation Syndromes

- refers to a subset of SVTs mediated by an accessory pathway which can lead to ventricular pre-excitation

AV Re-Entrant (or Reciprocating) Tachycardia (AVRT)

- re-entrant loop in antegrade via normal conduction system and retrograde via accessory pathway
- often in patients with an antegradely conducting bypass tract (WPW); may also occur if there is an exclusively retrogradely conducting (i.e. concealed) bypass tract - in these cases the ECG is normal and there are no delta waves. Note that most AVRT is orthodromic, therefore, retrograde conduction up the pathway is most common mechanistically initiated by a premature atrial or ventricular complex
- treatment
  - acute: treatment is similar to AVNRT but avoid long-acting AV nodal blockers (e.g. digoxin and verapamil)
  - long-term: for recurrent arrhythmias, ablation of the bypass tract is recommended
  - drugs such as flecainide and procainamide can be used

Wolff-Parkinson-White Syndrome

- congenital defect present in 1.5-2/1000 of the general population
- an accessory conduction tract (bundle of Kent; can be in RA or LA) abnormally allows early electrical activation of part of one ventricle
- impulses travel at a greater conduction velocity across the bundle of Kent thereby effectively 'bypassing' AV node
  - since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex the so-called "delta wave"
- atrial impulses that conduct to the ventricles through both the bundle of Kent and the normal AV node/His-Purkinje system generate a broad "fusion complex"
- ECG features of WPW
  - PR interval <120 msec
  - delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  - widening of the QRS complex due to premature activation
  - secondary ST segment and T wave changes
  - tachyarrhythmias may occur most often AVRT and AFib
- orthodromic AVRT: the most common arrhythmia in WPW stimulus from a premature complex travels up the bypass tract (ventricles to atria) and down the AV node (atria to ventricles) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system)
  - comprises 95% of the re-entrant tachycardias associated with WPW syndrome
- antidromic AVRT: more rarely, the stimulus goes up the AV node (ventricles to atria) and down the bypass tract (atria to ventricles); wide and abnormal QRS as ventricular activation is only via bypass tract

AFib in WPW Patients

- AFib is the index arrhythmia in up to 20% of patients with WPW syndrome
  - usually intermittent rather than persistent or permanent
- rapid atrial depolarizations in AFib are conducted antegradely through the bypass tract which is not able to filter impulses like the AV node can and thus the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens ("pre-excited AFib")
- treatment: electrical cardioversion, IV procainamide, or IV amiodarone
  - do not use drugs that slow AV node conduction during pre-excited AFib (e.g. digoxin, β-blockers) as this may cause preferential conduction through the bypass tract and increase the risk of VFib
    - note: even without drug administration, AFib with WPW can lead to VFib and would be an indication for an urgent EPS and ablation (especially with very rapid ventricular rates during AFib)
  - long-term: ablation of bypass tract

Ventricular Tachyarrhythmias

Premature Ventricular Contraction or Ventricular Premature Beat

- QRS width >120 msec, no preceding P wave, bizarre QRS morphology
- origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
- PVCs may be benign, but are usually significant in the following situations:
  - consecutive (≥3 = VT) or multiform (varied origin)
  - PVC falling on the T wave of the previous beat ("R on T phenomenon"): may precipitate VT or VFib
- risk of sustained arrhythmia depends on the clinical situation (i.e. MI, HF), not the PVCs themselves
- **treatment**
  - lifestyle changes (e.g. limiting or eliminating alcohol, caffeine, and stimulants) may be sufficient in patients with mild symptoms
  - in patients with more severe symptoms or underlying structural disease, β-blockers, catheter ablation, or antiarrhythmic therapy may be indicated

Accelerated Idioventricular Rhythm

- ectopic ventricular rhythm with rate of 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute MI or other types of heart disease (i.e. cardiomyopathy, HTN, valvular heart disease) but it does not affect prognosis and does not usually require treatment

Ventricular Tachycardia

- 3 or more consecutive ectopic ventricular complexes
  - rate >100 bpm (usually 140-200)
  - ventricular flutter: if rate approximately 300 bpm and monomorphic sinusoidal pattern
  - "sustained VT" if it lasts longer than 30 s
  - ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec)
  - AV dissociation, bizarre QRS pattern
  - also favour diagnosis of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
  - occasionally, during VT, supraventricular impulses may be conducted to the ventricles; these impulses generate QRS complexes with normal/aberrant supraventricular morphology (i.e. "ventricular capture") or summation pattern (i.e. "fusion complexes")
  - by itself, nonsustained VT (<30 s without hemodynamic collapse) independently increases mortality and cardiovascular events such as stroke; it can also indicate higher than usual risk of subsequent sustained VT, especially with structural heart disease
- **monomorphic VT**
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - can degenerate into polymorphic VT or VFib
  - typically result from intraventricular re-entry circuit, especially in patients with RV/LV dysfunction, may be idiopathic without any structural heart disease
  - potential causes: chronic infarct related scarring, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances
- **polymorphic VT**
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm)
  - potential causes: acute MI, severe or silent ischemia, valvular heart disease, HCM, dilated cardiomyopathies, myocarditis, congenital heart disease, WPW with anterograde accessory pathway, electrolyte or acid-base disturbances, and predisposing factors for QT prolongation

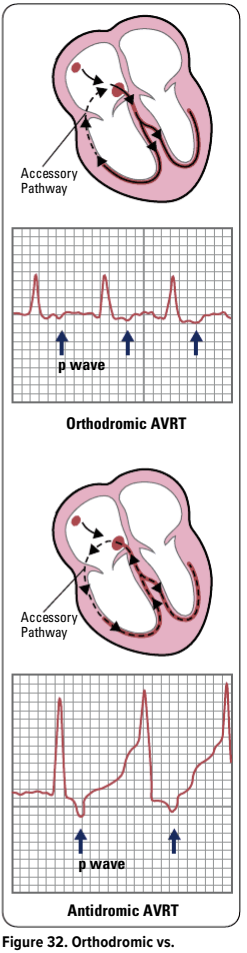


Figure 32. Orthodromic vs. antidromic AVRT

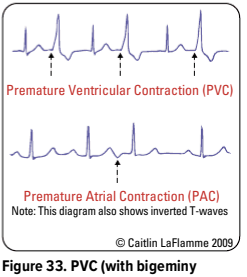

Premature Ventricular Contraction (PVC)
Premature Atrial Contraction (PAC)
Note: This diagram also shows inverted T-waves
© Caitlin LaFlamme 2009

Figure 33. PVC (with bigeminy pattern) and PAC. Note the difference between the normal QRS/T wave and the PVC-generated QRS/T wave

- **treatment**
  - sustained VT (>30 s) is an emergency requiring immediate treatment
  - hemodynamic compromise: treat VT with electrical cardioversion and ACLS
  - no hemodynamic compromise: treat VT with electrical cardioversion, amiodarone, Type IA agents (e.g. procainamide, quinidine)
  - every patient with sustained VT/VFib and comorbid structural heart disease, in the absence of reversible causes, should be considered for ICD implantation to prevent SCD

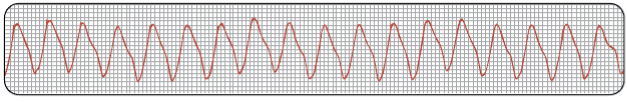


Figure 34. VT (monomorphic)

Table 7. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy*

Clinical Clues		ECG Clues	
Presenting symptoms	Not helpful	AV dissociation	VT
History of CAD and previous MI	VT	Capture or fusion beats	VT
Physical exam		QRS width >140 msec	VT
Cannon "a" waves Variable S1	VT	Extreme axis deviation (left or right superior axis)	VT
Carotid sinus massage/adenosine terminates arrhythmia	SVT**	Positive QRS concordance (R wave across chest leads)	VT
		Negative QRS concordance (S wave across chest leads)	May suggest VT
		Axis shift during arrhythmia	VT (polymorphic)

***If patient >65 yr and previous MI or structural heart disease, then chance of VT >95%**
**May terminate VT in some patients with no structural heart disease

Arrhythmias that may present as a Wide QRS Tachycardia
- VT (this is most common, especially in older patients or those with structural heart disease)
- SVT with aberrant conduction (rate related)
- SVT with pre-existing BBB or nonspecific intraventricular conduction defect
- AV conduction through a bypass tract in WPW patients during an atrial tachyarrhythmia (e.g. atrial flutter, atrial tachycardia)
- Antidromic AVRT in WPW patients (see *Pre-Excitation Syndromes, C25*)

Torsades de Pointes

- a variant of polymorphic VT that occurs in patients with baseline QT prolongation "twisting of the points"
- looks like usual VT except QRS complexes "rotate around the baseline," changing their axis and amplitude
- usually starts following a post extrasystolic pause ("pause dependent")
- ventricular rate >100 bpm, usually 150-300 bpm
  - usual onset after a post-PVC pause associated with "pause dependent" QT prolongation)
- etiology: occurs in association with prolonged QT intervals
  - congenital long QT syndromes
  - drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  - electrolyte disturbances: hypokalemia, hypomagnesemia
  - nutritional deficiencies causing above electrolyte abnormalities
- treatment: IV magnesium, temporary pacing ß blocker, correct the underlying cause of prolonged QT
  - electrical cardioversion and ACLS if hemodynamic compromise

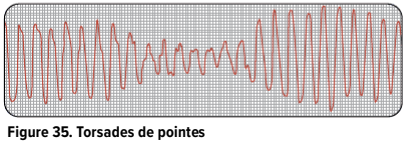


Figure 35. Torsades de pointes

Ventricular Fibrillation

- chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology without clear QRS complexes
- terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and CO, and electrical defibrillation is carried out
- most frequent cause of sudden death
- refer to ACLS algorithm for complete therapeutic guidelines

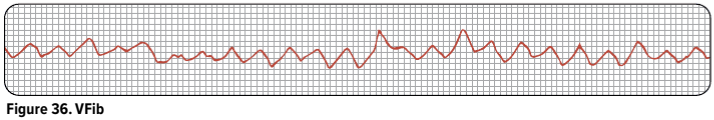


Figure 36. VFib

Sudden Cardiac Arrest

Definition

- cessation of cardiac electrical activity with circulatory collapse (loss of pulses) and gasping respirations or lack of spontaneous breathing
- patient becomes suddenly unresponsive
- presenting rhythms may be PEA, asystole, VFib (less commonly pulseless VT)

Etiology

- the likelihood of an underlying cardiac cause is proportional to age at time of arrest
  - cardiac causes (especially CAD) are more likely in older adults
  - non-cardiac causes are more likely in children and young adults (<35 yr)

Table 8. Etiology of Cardiac Arrest

Cardiac Causes		Non-Cardiac Causes	
myocardial Ischemia	STEMI NSTEMI Coronary spasm coronary dissection Anomalous coronary artery	**Vascular**	Pulmonary embolism Aortic dissection Aortic rupture Stroke
Ischemic Cardiomyopathy	HF Scar	**Neurologic**	Sudden unexplained death in epilepsy Neurogenic
Non-Ischemic Cardiomyopathy	Dilated CM Hypertrophic CM Infiltrative CM myocarditis Arrhythmogenic RV CM Hypertensive CM VHD with LV failure	**Hemorrhagic**	Subarachnoid Intracranial Gastrointestinal
Valvular Heart Disease	AS MR	**Infection**	Sepsis Pneumonia
Heritable ion channel disorders	Long QT syndrome Brugada syndrome	**Respiratory**	Respiratory arrest Tension pneumothorax
Primary Arrhythmogenic	Acquired QT prolongation Idiopathic Complete heart block WPW	**Other**	Substance overdose Ketoacidosis Trauma
Congenital Heart Disease	Tetralogy of Fallot VSD Post-Surgical scar		

Management

- acute: resuscitate according to ACLS guidelines (see Anesthesia, A32)
  - resuscitation can be grouped into those with and without shockable rhythms
  - activation of emergency systems and high-quality chest compressions are essential for any bystander
- investigate underlying causes using cardiac catheterization, electrophysiologic studies, echocardiography
  - patients with ST-elevation require emergent coronary angiography and revascularization
  - patients without ST-elevation can still have clinically relevant coronary lesions and therefore benefit from coronary angiography on a non-emergent basis
- initiate targeted temperature management to optimize neurologic recovery regardless of presenting rhythm
- treat underlying cause
- antiarrhythmic drug therapy: amiodarone, lidocaine, β-blockers
- ICD for secondary prevention

See Landmark Cardiology and Cardiac Surgery Trials table for more information on COACT, which details the 1-yr clinical outcomes of angiography timing on survival in resuscitated cardiac arrest patients without STEMI.

Electrophysiologic Studies

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of SA node dysfunction and localize site of AV conduction block (rarely performed)
- tachyarrhythmias: map for possible ablation, assess inducibility of VT prior to ICD implant

Electrical Pacing

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia with intermittent bradycardia precluding rate limiting medications

Pacemaker Indications

- SA node dysfunction (most common): symptomatic bradycardia ± hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

Pacemaker Complications

- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism), pacemaker leads (perforation, malposition), pocket hematomas, and infection; rarer complications include venous stenosis or thrombosis, and tricuspid regurgitation
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure, pacemaker syndrome, lead fractures, and pacemaker-mediated tachycardia (note: PMT is benign and self-limited, though may be bothersome to patients)

Pacing Techniques

- temporary: transvenous (jugular, subclavian, femoral) or external (transcutaneous) pacing
- permanent: transvenous into RA, apex of RV, or both
- single or dual chamber: can sense and pace atrium, ventricle, or both
- rate responsive, able to respond to physiologic demand
- biventricular pacing (cardiac resynchronization therapy): leads are guided to RV and LV to stimulate both ventricles

Implantable Cardioverter Defibrillators

- SCD usually results from VFib, sometimes preceded by monomorphic or polymorphic VT
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention and selected patients for primary prevention
- CRT-D may be of benefit in patients with LBBB, prolonged QRS, and LVEF <35%
- see *Heart Failure, C40* for current treatment recommendations

Catheter Ablation

Modalities

- radiofrequency (RF) ablation: a low-voltage high-frequency form of electrical energy (similar to cautery); RF ablation produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth
- cryoablation: technology which uses a probe with a tip that decreases in temperature to -20˚C and -70˚C; small necrotic lesions are produced in a similar fashion to RF ablation; when brought to -20˚C, the catheter tip reversibly freezes the area; when brought to -70˚C for 5 min, it permanently scars the tissue
  - advantage: can "test" areas before committing to an ablation
  - disadvantage: takes much longer than RF (5 min per cryoablation vs. 1 min per RF ablation)
  - cryoablation is most commonly used for AFib

Indications

- paroxysmal SVT
  - AVNRT: accounts for more than half of all cases; slow AV nodal pathway is targeted for ablation in these cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
  - re-entrant rhythm with an accessory AV connection as one of the limbs
  - corrected by targeting the accessory pathway
- atrial flutter: re-entry circuit in RA
- AFib: primarily isolation of pulmonary vein triggers, usually with additional ablation in the atrial chambers
- idiopathic VT: focus arises from the right ventricular outflow tract or left ventricular outflow tract and less commonly originates in the inferoseptal LV near the apex
  - scar mediated VT most commonly due to scarring from previous MI or other cardiomyopathies; ablation less often successful and not first line therapy
  - significant benefit was seen with catheter ablation vs. antiarrhythmic drug escalation among patient with amiodarone-resistant VT, in contrast to non-amiodarone resistant VT

Major Complications
- cardiac: high grade AV block requiring permanent pacemaker (less risk with cryoablation), new or worsening arrhythmia, tamponade, pericarditis
- vascular: hematoma, vascular injury, thromboembolism, TIA/stroke
- pulmonary: PE

Ischemic Heart Disease

Epidemiology
- refer to CCS guidelines - 2014 Stable Ischemic Heart Disease Guidelines for Diagnosis and Management for more information
- most common cause of cardiovascular morbidity and mortality
- patients may have asymptomatic or symptomatic disease
- silent myocardial ischemia may be a predictor of adverse coronary events and cardiac mortality
  - needs to be monitored via intracardiac monitoring of physiological and hemodynamic parameters, metabolic indicators of ischemia in the coronary sinus, and hemodynamic factors
  - optimal medical therapy (reduction of HR and BP) and myocardial revascularization
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- M:F=2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70
  - CHD incidence in women triples shortly after menopause
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease see Family Medicine, FM8

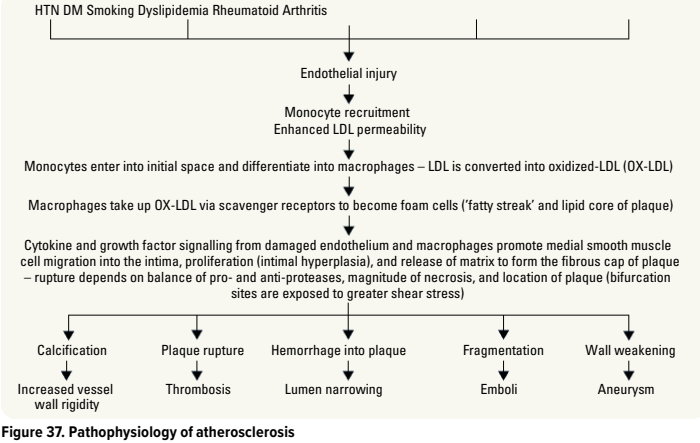

HTN DM Smoking Dyslipidemia Rheumatoid Arthritis
Endothelial injury
Monocyte recruitment
Enhanced LDL permeability
Monocytes enter into initial space and differentiate into macrophages – LDL is converted into oxidized-LDL (OX-LDL)
Macrophages take up OX-LDL via scavenger receptors to become foam cells ('fatty streak' and lipid core of plaque)
Cytokine and growth factor signalling from damaged endothelium and macrophages promote medial smooth muscle cell migration into the intima, proliferation (intimal hyperplasia), and release of matrix to form the fibrous cap of plaque – rupture depends on balance of pro- and anti-proteases, magnitude of necrosis, and location of plaque (bifurcation sites are exposed to greater shear stress)
Calcification
Plaque rupture
Hemorrhage into plaque
Fragmentation
Wall weakening
Increased vessel wall rigidity
Thrombosis
Lumen narrowing
Emboli
Aneurysm

Figure 37. Pathophysiology of atherosclerosis

Table 9. Risk Factors and Markers for Atherosclerotic Heart Disease

Non-Modifiable Risk Factors	Modifiable Risk Factors §	Markers of Disease
Age	Hyperlipidemia*	Elevated high-sensitivity C-reactive protein (hsCRP)
Male, postmenopausal female	HTN*	Coronary artery calcification
Family history (FHx) of MI*	DM*	Carotid IMT/plaque
First degree male relative <55 yr	Cigarette smoking*	Ankle-brachial index
First degree female relative <65 yr	Psychosocial stress	
	Abdominal obesity	
	Sedentary lifestyle	
	Heavy alcohol intake	
	Not consuming fruits and vegetables daily	
	Elevated lipoprotein(a)	
	Hyperhomocysteinemia	

* Major risk factors
§ Modifiable risk factors account for >90% of MIs

Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHEMIA)
NEJM 2020;382:1395-1407
Purpose: Assess clinical outcomes in stable coronary disease treated with invasive plus medical therapy vs. medical therapy alone.
Methods: 5179 patients were randomized to invasive therapy (angiography and revascularization) plus medical therapy or medical therapy alone plus angiography upon failure of initial conservative approach. The primary outcome was a composite of mortality from CV causes, MI, hospitalization for UA, HF or resuscitated cardiac arrest.
Results: Over a median of 3.2 yr, 318 and 352 primary outcome events occurred in the invasive-strategy and conservative-strategy groups, respectively. At 5 yr, the cumulative event rate was 16.4% and 18.2% in the invasive-strategy and conservative-strategy groups, respectively.
Conclusion: In patients with chronic stable coronary disease, there was no evidence that an initial invasive strategy reduced ischemic CV events or death from any cause over a median of 3.2 yr, compared with initial conservative medical therapy.

Chronic Stable Angina

Definition

- symptom complex resulting from an imbalance between oxygen supply and myocardial oxygen demand in the myocardium

Etiology and Pathophysiology

- factors that decrease myocardial oxygen supply:
  - decreased luminal diameter: atherosclerosis, vasospasm
  - decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - decreased hemoglobin: anemia
  - decreased SaO_2: hypoxemia
  - congenital anomalies
- factors that increase myocardial oxygen demand:
  - increased HR: hyperthyroidism, exercise, anemia, pregnancy
  - increased contractility: hyperthyroidism
  - increased wall stress: myocardial hypertrophy, AS

Chronic stable angina is most often due to a fixed stenosis caused by an atheroma
ACSs are the result of plaque rupture which causes a cascade resulting in thrombosis

Signs and Symptoms

- typical
  1. retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety
  2. predictably precipitated by the "3 Es": exertion, emotion, eating
  3. brief duration, lasting <10-15 min and typically relieved by rest and nitrates
- atypical/probable angina (meets 2 of the above)
- non-cardiac chest pain (meets none or 1 of the above)
- Levine's sign: clutching fist over sternum when describing chest pain
- anginal equivalents: dyspnea, acute LV failure, flash pulmonary edema
- ischemia may present differently in understudied populations

Canadian Cardiovascular Society (CCS) Functional Classification of Angina

Class I: ordinary physical activity (walking, climbing stairs) does not cause angina; angina with strenuous, rapid, or prolonged activity

Class II: slight limitation of ordinary activity: angina brought on at >2 blocks on level or climbing >1 flight of stairs, or by emotional stress

Class III: marked limitation of ordinary activity: angina brought on at <2 blocks on level or climbing <1 flight of stairs

Class IV: inability to carry out any physical activity without discomfort; angina may be present at rest

Clinical Assessment

- history including directed risk factor assessment and physical exam
- labs: Hb, fasting glucose, fasting lipid profile, HbA1c, renal function tests, liver function tests, and thyroid function test
- 12-lead ECG (at rest and during episode of chest pain if possible)
- CXR (suspected HF, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs/symptoms of pulmonary disease)
- stress testing (see *Stress Testing, C15*) or angiography
- echo for other causes of chest pain:
  - aortic dissection
  - valvular heart disease
  - HCM
  - LV dysfunction and/or wall motion abnormality
  - pericardial disease/effusion

Differential Diagnosis

- see *Differential Diagnoses of Common Presentations, C5*

Treatment of Chronic Stable Angina

- refer to 2019 European Society of Cardiology guidelines for more information

1. General Measures

- goals: to reduce myocardial oxygen demand and/or increase oxygen supply
- lifestyle modification (diet, exercise, smoking cessation)
- treatment of risk factors: e.g. statins (see Endocrinology, E5, Family Medicine, FM11 for target lipid guidelines), antihypertensives
- pharmacological therapy to stabilize the coronary plaque which will prevent rupture and thrombosis

2. Antiplatelet Therapy (first-line therapy)

- ASA
- clopidogrel when ASA contraindicated
- low dose rivaroxaban in combination with ASA (based on COMPASS trial)

3. β-blockers (first-line therapy improves survival in patients with HTN)

- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β2 receptors)
- avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand

Aspirin in the Primary Prevention of Cardiovascular Disease on Diabetic Patients: Systematic Review and Meta-analysis
Primary Care Diabetes. 2020;14(3):213-21
Purpose: This study sought to conduct a systematic review of all randomized controlled trials that assessed the clinical effects of aspirin in diabetic patients for primary prevention purposes.
Methods: A comprehensive search was conducted in MEDLINE, EMBASE, and CENTRAL for RCTs examining the effects of aspirin in diabetic patients for primary prevention. The primary outcomes were all-cause mortality and the composite outcome of major adverse cardiovascular events.
Results: No significant reduction in all-cause mortality was found (RR 0.96, 95% CI 0.90-1.03; 7 RCTs; 27595 patients). However, there was an 8% risk reduction in major adverse cardiovascular events (RR 0.92, 95% CI 0.84-0.999; 8 RCTs; 29814 patients). The risks of major bleeding (RR 1.30, 95% CI 1.10-1.53; 2 RCTs, 18019 patients) and major gastrointestinal bleeding (RR 1.39, 95% CI 1.08-1.80; 2 RCTs, 18019 patients) were significantly increased.
Conclusions: The use of aspirin in primary prevention for diabetic patients was linked to an increased risk of major bleeding, a modest reduction in major adverse cardiovascular events, and no observed benefit in terms of mortality

4. Nitrates (symptomatic control, no clear impact on survival)
- decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
- maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)

5. Calcium Channel Blockers (CCBs, second-line or combination)
- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- caution: verapamil/diltiazem combined with β-blockers may cause symptomatic sinus bradycardia or AV block
- contraindicated in patients with LV systolic dysfunction

6. Renin-Angiotensin-Aldosterone System Blockade
- angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. HTN, DM, proteinuric renal disease, previous MI with LV dysfunction)
- ARB can be considered in patients intolerant to ACEI
- benefit in all patients at high-risk for CV disease (e.g. those with concomitant DM, renal dysfunction, or LV systolic dysfunction)

7. Invasive Strategies
- revascularization (see *Coronary Revascularization, C37*)

Variant Angina (Prinzmetal's Angina)
- Myocardial ischemia secondary to coronary artery vasospasm with or without atherosclerosis
- uncommonly associated with infarction or LV dysfunction
- typically occurs between midnight and 8 am, unrelated to exercise, relieved by nitrates
- typically ST elevation is observed on ECG
- diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
- treat with nitrates and CCBs
- strongly recommend patient to stop smoking

Syndrome X
- Typical symptoms of angina but normal angiogram
- may show definite signs of ischemia with exercise testing
- thought to be due to inadequate vasodilator reserve of coronary resistance vessels
- better prognosis than overt epicardial atherosclerosis

Acute Coronary Syndromes

Definition
- ACS includes the spectrum of UA, NSTEMI, and STEMI; this distinction aids in providing the appropriate therapeutic intervention
  - UA is clinically defined by any of the following:
    - accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion, decreased response to treatment
    - angina at rest
    - new-onset angina
    - angina post-MI or post-procedure (e.g. PCI, CABG)
  - MI (STEMI/NSTEMI) is defined by evidence of myocardial necrosis and is diagnosed by a rise/fall of serum markers plus any one of:
    - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
    - ECG changes (ST-T changes, new BBB, or pathological Q waves)
    - imaging evidence (myocardial loss of viability, wall motion abnormality, or intracoronary thrombus)
    - if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
  - NSTEMI meets criteria for MI without ST elevation or BBB
  - STEMI meets criteria for MI characterized by ST elevation or new BBB
- possible ACS in women, diabetics, and older adults is more likely to present with "atypical" symptoms such as dyspnea or weakness even in the presence of acute coronary-related ischemia

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction (COLCOT)
NEJM 2019;381:2497-2505
Purpose: To determine if colchicine lowers risk of future CV events following MI.
Methods: Patients (n=4745) who had an MI within the last 30 d were randomized to colchicine once daily or placebo. The primary efficacy endpoint was a composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina.
Results: Median follow-up was 22.6 mo. The primary endpoint occurred in 5.5% and 7.1% of patients in the colchicine and placebo groups, respectively (P=0.02). Pneumonia was observed in 0.9% of the patients in the colchicine group and in 0.4% of patients in the placebo group (P=0.03).
Conclusion: In patients with recent MI, colchicine lowered the risk of subsequent CV events as compared to placebo.

Investigations
- history and physical
  - note that up to 30% of MIs are unrecognized or "silent" due to atypical symptoms that are more common in women, patients with DM, elderly, post-heart transplant (because of denervation)
- ECG
- CXR

- labs
  - serum cardiac biomarkers for myocardial damage (use of high-sensitive cardiac troponin (hs-cTn) with a validated 0 h/2 h algorithm recommended blood sampling at 0 h and 2 h) (see *Cardiac Biomarkers, C13*)
  - CBC, International Normalized Ratio (INR)/prothrombin time test (PTT), electrolytes, magnesium, creatinine, urea, glucose, and serum lipids
  - draw serum lipids within 24-48 h because values are unreliable from 2-48 d post-MI

MANAGEMENT OF ACUTE CORONARY SYNDROMES

1. General Measures
- ABCs: assess and correct hemodynamic status first
- bed rest, cardiac monitoring, oxygen
- nitroglycerin sublingual (SL) followed by IV
- morphine IV

2. Antiplatelet and Anticoagulation Therapy
- see also 2018 CCS/CAIC Antiplatelet Guidelines, 2012 and 2010 CCS Antiplatelet Guidelines, and 2009 CCS Position Statement on Dual Antiplatelet Therapy in Patients Requiring Urgent CABG for details (free mobile apps available on iOS and Android platforms in the CCS app stores). Also see 2020 ESC guidelines on ACS management in patients without persistent ST-segment elevation, 2017 ESC guidelines on STEMI management, and 2019 CCS guidelines on acute STEMI management (focused update on regionalization and reperfusion)
- ASA chewed
- NSTEMI
  - ticagrelor + ASA + LMWH/IV unfractionated heparin (UFH), unless contraindications
    - LMWH, except in renal failure or if CABG is planned, within 24 h
    - fondaparinux also commonly used in Canada for initial medical management of NSTEMI/UA based on OASIS-5 results
  - clopidogrel used if patient ineligible for ticagrelor
- if PCI is planned: ticagrelor or prasugrel and consider IV glycoprotein IIb/IIIa inhibitor (e.g. eptifibatide, tirofiban)
  - clopidogrel used if patient ineligible for ticagrelor and prasugrel
  - prasugrel contraindicated in those with a history of stroke/TIA, and its avoidance or lower dose is recommended for those >75 yr or weighing <60 kg (TRITON-TIMI 38)
- anticoagulation options depend on reperfusion strategy:
  - primary PCI: UFH during procedure; bivalirudin is a possible alternative
  - thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
  - no reperfusion: LMWH (enoxaparin) until discharge from hospital
- continue LMWH or UFH followed by oral anticoagulation at discharge if at high-risk for thromboembolic event (large anterior MI, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)
  - in patients with AFib (CHA2DS2-VASc score ≥1 in men and ≥2 in women), use triple antithrombotic therapy for up to 1 wk and then transition to dual antithrombotic therapy (using a NOAC and an antiplatelet agent (preferably clopidogrel))

3. β-blockers
- STEMI: contraindications include signs of HF, low output states, risk of cardiogenic shock, heart block, asthma, or airway disease; initiate orally within 24 h of diagnosis when indicated
- if β-blockers are contraindicated or if β-blockers/nitrates fail to relieve ischemia, non-dihydropyridine CCB (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (CCB do not prevent MI or decrease mortality)

4. Invasive Strategies and Reperfusion Options
- UA/NSTEMI: early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  - diagnosis of NSTEMI
  - recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  - CHF or LV dysfunction
  - hemodynamic instability
  - high (≥3) Thrombolysis in Myocardial Infarction (TIMI) risk score (tool used to estimate mortality following an ACS)
  - GRACE risk score >140
  - sustained ventricular tachycardia
  - dynamic ECG changes, transient ST-elevation
  - high-risk findings on non-invasive stress testing
  - PCI within the previous 6 mo
  - repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high-risk features
  - note: thrombolysis is NOT administered for UA/NSTEMI

Complete Revascularization with Multivessel PCI for Myocardial Infarction (COMPLETE)
NEJM 2019;381:1411-1421
Purpose: To determine if PCI of non-culprit lesions, in addition to culprit lesions, further reduces the risk of CV events or MI in patients with STEMI.
Methods: Patients with STEMI and multivessel CAD who had undergone culprit-lesion PCI (n=4041) were randomized to either complete revascularization with PCI (of significant non-culprit lesions) or no further revascularization. The two main outcomes measured included: 1) the composite of CV death or MI, and 2) the composite of CV death, MI, or ischemia-driven revascularization.
Results: The first outcome was observed in 7.8% of the complete revascularization group and 10.5% of the culprit-lesion-only PCI group (P=0.004). The second outcome was observed in 8.9% of the complete revascularization group and 16.7% of the culprit-lesion-only PCI group (P<0.001).
Conclusions: In patients with STEMI and multivessel CAD, complete revascularization by PCI further reduced the risk of CV death or MI as compared to culprit-lesion-only PCI.

TIMI Risk Score for UA/NSTEMI

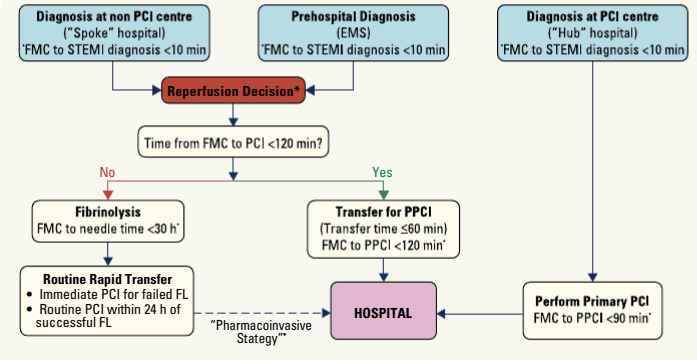
Characteristics	Points
Historical	
Age ≥65 yr	1
≥3 risk factors for CAD	1
Known CAD (stenosis ≥50%)	1
Aspirin ® use in past 7 d	1
Presentation	
Recent (≤24 h) severe angina	1
ST-segment deviation ≥0.5 mm	1
Increased cardiac marker	1

Risk Score = Total Points
If TIMI risk score ≥3 , consider early LMWH and angiography
TIMI = thrombolysis in myocardial infarction
UA = unstable angina
JAMA 2000;284:835-842

- STEMI
  - after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - goal is to re-perfuse artery: thrombolysis ("EMS-to-needle") within 30 min or primary PCI ("EMS-to-balloon") within 90 min (if available)
  - PCI
    - early PCI (≤12 h after symptom onset and <90 min after presentation) improves mortality vs. thrombolysis with fewer intracranial hemorrhages and recurrent MIs
    - primary PCI: without prior thrombolytic therapy method of choice for reperfusion in experienced centres
    - rescue PCI: following failed thrombolytic therapy (diagnosed when ST segment elevation fails to resolve below half its initial magnitude after thrombolysis and patient still has chest pain)

    thrombolysis
    - assuming no contraindications, use if <12 h since symptom onset and primary PCI cannot be conducted within 120 min of STEMI diagnosis
    - note: benefit of thrombolysis is inversely proportional to time from symptom onset; in patients meeting the above criteria, the later the presentation (>3 h), the more one should consider using primary PCI instead (depending on clinical circumstances)

Newer, more accurate risk quantification scores for UA/NSTEMI exist, such as the GRACE Risk Score; however, TIMI is still used most often



*Also consider clinical factors such as symptom duration and presence of contraindications to fibrinolysis
EMS = emergency medical services; FL = fibrinolysis; FMC = first medical contact; PCI = percutaneous coronary intervention; PPCI = primary percutaneous coronary intervention. Guideline based recommendations: strong = " ; weak = #

Figure 38. Reperfusion strategy in STEMI

Table 10. Contraindications for Thrombolysis in STEMI

Absolute	Relative
Prior intracranial hemorrhage	Chronic, severe, poorly controlled HTN
Known structural cerebral vascular lesion	Uncontrolled HTN (sBP >180, dBP >110)
Known malignant intracranial neoplasm	Current anticoagulation
Significant closed-head or facial trauma (≤3 mo)	Noncompressible vascular punctures
Ischemic stroke (≤3 mo)	Ischemic stroke (≥3 mo)
Active bleeding	Recent internal bleeding (≤2-4 wk)
Suspected aortic dissection	Prolonged CPR or major surgery (≤3 wk)
	Pregnancy
	Active peptic ulcer disease

Long-Term Management of ACS

- risk of progression to MI, or recurrence of MI, or death is highest within 1 mo
- at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- pre-discharge workup: ECG and echo to assess residual LV systolic function
- drugs required in hospital to control ischemia should be continued after discharge in all patients
- other medications for long-term management of ACS are summarized below

1. General Measures

- education
- risk factor modification

2. Antiplatelet and Anticoagulation Therapy
- see also CCS Antiplatelet Guidelines 2018 for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
- ECASA 81 mg daily
- ticagrelor 90 mg BID or prasugrel 10 mg daily (at least 1 mo, up to 9-12 mo; if stent placed at least 12 mo)
- clopidogrel 75 mg daily can be used as alternatives to ticagrelor and prasugrel when indicated
- ± warfarin x 3 mo if high-risk (high-risk patients include those with large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)
- rivaroxaban 2.5 mg BID (based on COMPASS trial)

3. β-Blockers (e.g. metoprolol 25-50 mg BID or atenolol 50-100 mg daily)

4. Nitrates
- alleviate ischemia but do not improve outcome
- use with caution in right-sided MI patients who have become preload dependent

5. Calcium Channel Blockers (NOT recommended as first line treatment, consider as alternative to β-blockers)

6. ACEIs
- prevent adverse ventricular remodelling
- recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
- recommended for symptomatic CHF, reduced LVEF (<40%), anterior MI
- use ARBs in patients who are intolerant of ACEI; avoid combining ACEI and ARB

7. ± Aldosterone Antagonists
- if already on ACEI and β-blockers, with and LVEF <40% and CHF or DM
- significant mortality benefit shown with eplerenone by 30 d

8. Lipid Lowering Therapy Statins (e.g. atorvastatin 80 mg daily)
- second line add-on therapy: ezetimibe or PCSK9 inhibitor
- as per CCS 2022 Dyslipidemia Guidelines, decision on which therapy to initiate can be based on achieved LDL (target is <1.8 mmol/L)

9. Invasive Cardiac Catheterization if indicated (risk stratification)

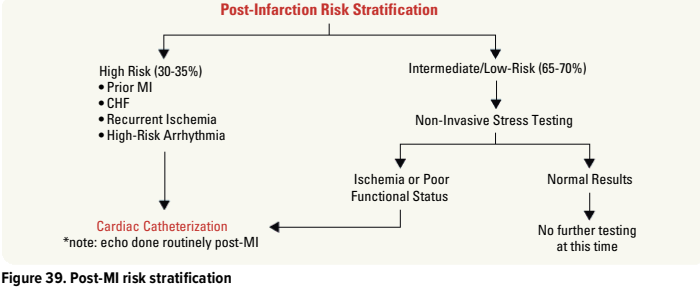


Figure 39. Post-MI risk stratification

Prognosis following STEMI

- 5-15% of hospitalized patients will die
  - risk factors
    - infarct size/severity
    - age
    - comorbid conditions
    - development of HF or hypotension
- post-discharge mortality rates
  - 6-8% within first year, half of these within first 3 mo
  - 4% per year following first yr
  - risk factors
    - LV dysfunction
    - residual myocardial ischemia
    - ventricular arrhythmias
    - history of prior MI

Is this Patient having a MI?
From The Rational Clinical Examination
JAMA 1998;381(14):1256-1263
Study: Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of an acute MI.
Results: In patients with normal or non-diagnostic ECG, no established CAD, and prolonged or recurrent chest pain typical of their usual discomfort, radiation of pain to the shoulder OR both arms had the highest positive likelihood ratio (+LR) of 4.1 and a negative likelihood ratio (-LR) of 0.68. Radiation to the right arm had a +LR of 3.8 and –LR of 0.86, vomiting had a +LR of 3.5 and –LR of 0.87, while radiation to the left arm only had a +LR of 1.3 and a –LR of 0.9.
Conclusions: The most compelling features that increase likelihood of an MI are ST-segment and cardiac enzyme elevation, new Q-wave, and presence of an S3 heart sound. In patients where the diagnosis of MI is uncertain, radiation of pain to the shoulder OR both arms, radiation to the right arm, and vomiting had the best predictive values, while radiation to the left arm is relatively non-diagnostic.

Complications of MI

CRASH PAD
Cardiac Rupture
Arrhythmia
Shock
Hypertension/Heart failure
Pericarditis/Pulmonary embolism
Aneurysm
DVT

Resting LVEF is a useful prognostic factor

Table 11. Complications of MI

Complication	Etiology	Presentation	Therapy
Arrhythmia			See *Arrhythmias, C19*
1. Tachycardia	Sinus, AFib, VT, VFib	First 48 h	
2. Bradycardia	Sinus, AV block	First 48 h	
Myocardial Rupture			
1. LV free wall	Transmural infarction	1-7 d	Surgery
2. Papillary muscle (→ MR)	Inferior infarction	1-7 d	Surgery
3. Ventricular septum (→ VSD)	Septal infarction	1-7 d	Surgery
Shock/CHF	Infarction or aneurysm	Within 48 h	Inotropes, intra-aortic balloon pump
Post-Infarct Angina	Persistent coronary stenosis	Anytime	Aggressive medical therapy
	Multivessel disease		PCI or CABG
Recurrent MI	Reocclusion	Anytime	Aggressive medical therapy
			PCI or CABG
Thromboembolism	Mural/apical thrombus DVT	7-10 d, up to 6 mo	Anticoagulation
Pericarditis	Inflammatory	1-7 d	ASA
Dressler's Syndrome	Autoimmune	2-8 wk	

Treatment of NSTEMI

BEMOAN
β-blocker
Enoxaparin
Morphine
O$_2$
ASA
Nitrates

Treatment Algorithm for Acute Coronary Syndrome

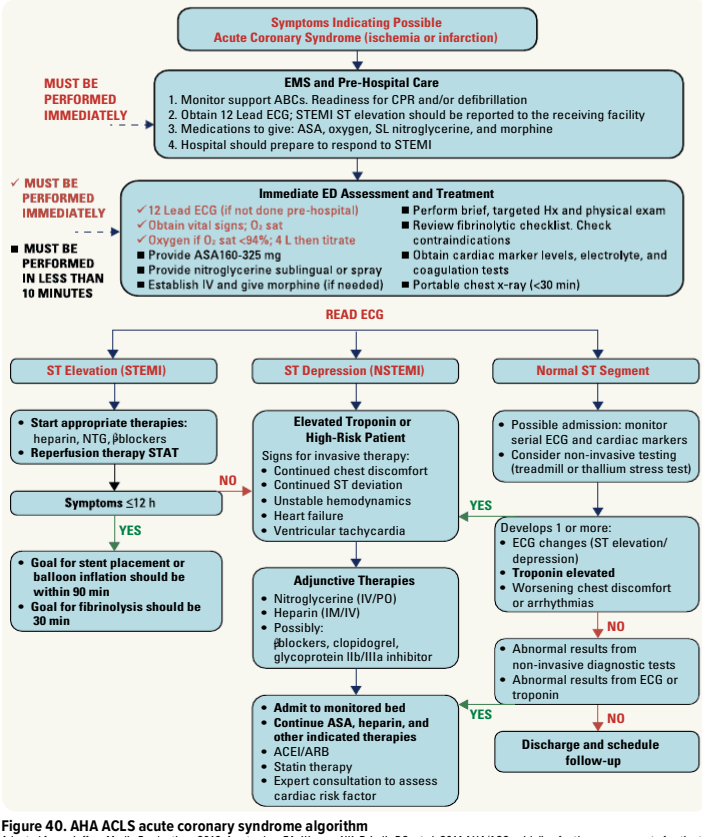

Symptoms Indicating Possible Acute Coronary Syndrome (ischemia or infarction)
MUST BE PERFORMED IMMEDIATELY
EMS and Pre-Hospital Care
1. Monitor support ABCs. Readiness for CPR and/or defibrillation
2. Obtain 12 Lead ECG; STEMI ST elevation should be reported to the receiving facility
3. Medications to give: ASA, oxygen, SL nitroglycerine, and morphine
4. Hospital should prepare to respond to STEMI
✓ MUST BE PERFORMED IMMEDIATELY
■ MUST BE PERFORMED IN LESS THAN 10 MINUTES
Immediate ED Assessment and Treatment
✓ 12 Lead ECG (if not done pre-hospital)
✓ Obtain vital signs; O₂ sat
✓ Oxygen if O₂ sat <94%; 4 L then titrate
■ Provide ASA160-325 mg
■ Provide nitroglycerine sublingual or spray
■ Establish IV and give morphine (if needed)
■ Perform brief, targeted Hx and physical exam
■ Review fibrinolytic checklist. Check contraindications
■ Obtain cardiac marker levels, electrolyte, and coagulation tests
■ Portable chest x-ray (<30 min)
READ ECG
ST Elevation (STEMI)
ST Depression (NSTEMI)
Normal ST Segment
• Start appropriate therapies: heparin, NTG, βblockers
• Reperfusion therapy STAT
Symptoms ≤12 h
NO
YES
• Goal for stent placement or balloon inflation should be within 90 min
• Goal for fibrinolysis should be 30 min
Elevated Troponin or High-Risk Patient
Signs for invasive therapy:
• Continued chest discomfort
• Continued ST deviation
• Unstable hemodynamics
• Heart failure
• Ventricular tachycardia
Adjunctive Therapies
• Nitroglycerine (IV/PO)
• Heparin (IM/IV)
• Possibly: βblockers, clopidogrel, glycoprotein IIb/IIIa inhibitor
• Admit to monitored bed
• Continue ASA, heparin, and other indicated therapies
• ACEI/ARB
• Statin therapy
• Expert consultation to assess cardiac risk factor
• Possible admission: monitor serial ECG and cardiac markers
• Consider non-invasive testing (treadmill or thallium stress test)
YES
Develops 1 or more:
• ECG changes (ST elevation/depression)
• Troponin elevated
• Worsening chest discomfort or arrhythmias
NO
• Abnormal results from non-invasive diagnostic tests
• Abnormal results from ECG or troponin
YES
NO
Discharge and schedule follow-up

Figure 40. AHA ACLS acute coronary syndrome algorithm
Adapted from: Jeffery Media Productions 2016. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. Circulation. 2014 Jan 1:CIR-0000000000000134

Contraindications to nitrates: severe aortic stenosis, hypertrophic cardiomyopathy, suspected right ventricular infarct, hypotension, marked bradycardia or tachycardia, and recent use of phosphodiesterase 5 inhibitors.

Coronary Revascularization

PERCUTANEOUS CORONARY INTERVENTION

- interventional cardiology technique aimed at relieving significant coronary artery stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

Indications

- medically refractory angina
- NSTEMI/UA with high-risk features (e.g. high TIMI risk score)
- primary/rescue PCI for STEMI
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG

Balloon Angioplasty and Intracoronary Stenting

- coronary lesions dilated with balloon inflation
- major complication is restenosis (approximately 15% at 6 mo), thought to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
  - bare metal stent (BMS) vs. drug-eluting stents: PRAMI trial demonstrated stenting non-culprit lesions results in 14% absolute risk reduction of cardiac death, nonfatal MI, or refractory angina
  - coated with antiproliferative drugs (sirolimus, paclitaxel, everolimus, zotarolimus)
  - reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
  - complication: late stent thrombosis (5 events per 1000 stents implanted)

Adjunctive Therapies

- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
  - dual antiplatelet therapy (ASA and clopidogrel or ticagrelor) for 6 mo (and up to 1 yr)
  - consider short-duration DAPT for 1 mo with BMS or 3 mo with DES followed by monotherapy for 12 mo among patients with high ischemic or bleeding risk
  - ASA and prasugrel can be considered for those at increased risk of stent thrombosis

Procedural Complications

- mortality and emergency bypass rates <1%
- nonfatal MI: approximately 2-3%

CORONARY ARTERY BYPASS GRAFT SURGERY

- objective of CABG is complete revascularization of the myocardium

Indications

- ≥50% diameter stenosis in the left main coronary artery
- ≥70% diameter stenosis in three major coronary arteries
- ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
- survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery
- ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
- ≥70% diameter stenosis in the proximal LAD artery and evidence of extensive ischemia
- multivessel CAD in patients with diabetes
- LV systolic dysfunction (LVEF 35% to 50%) and with significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization
- one or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

Contraindications

- CABG may be contraindicated in patients who are: elderly/frail, have multiple comorbidities or, for any other reason, may not survive surgery
- CABG may be contraindicated in patients who do not have myocardial viability
- CABG is contraindicated in patients that lack bypassable vessels

Results

- perioperative and in-hospital mortality rate after CABG: ~1% for the lowest risk elective patients, and 2% for all patients (depends on patient characteristics and heart function)
- predictive variables for early hospital mortality include older age (>80 yr), female sex, urgency of operation, left main stem disease, increasing extent of CAD, increasing LV dysfunctions, redo CABG

See Landmark Cardiology and Cardiac Surgery Trials table for more information on EXCEL which details the long-term efficacy profile of CABG vs. PCI in patients with left main CAD.

Ticagrelor with or without Aspirin® in High-Risk Patients after PCI
NEJM 2019;381:2032-2042
Purpose: To determine if monotherapy with ticagrelor, a P2Y12 inhibitor, after a period of dual antiplatelet therapy reduces the risk of bleeding following PCI.
Methods: Patients who were at high-risk for bleeding or an ischemic event underwent PCI and 3 mo of treatment with ASA plus ticagrelor. Patients (n=7119) were then randomized to receive either ticagrelor plus ASA or ticagrelor plus placebo for a year. The primary endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding.
Results: The primary endpoint was observed in 4.0% of patients in the ticagrelor plus placebo group and 7.1% of patients in the ticagrelor plus ASA group (P<0.001). The incidence of death from any cause, nonfatal MI, or nonfatal stroke was 3.9% in both groups (P<0.001 for noninferiority).
Conclusion: Among high-risk bleed patients who received PCI and 3 mo of dual antiplatelet therapy, additional ticagrelor monotherapy was associated with lower incidence of bleeding and the same risk of death, as compared to ticagrelor plus ASA therapy.

Safety and Efficacy Outcomes of Double vs. Triple Antithrombotic Therapy in Patients with Atrial Fibrillation Following Percutaneous Coronary Intervention
Eur Heart J 2019; 40:3757-3767
Purpose: To evaluate the safety and efficacy of double vs. triple antithrombotic therapy (DAT vs. TAT) in patients with AFib and ACS following PCI.
Methods: Systematic review and meta-analysis of 4 trials with a total of 10234 patients.
Conclusions: DAT was associated with lower risk of bleeding, but higher risk of stent thrombosis and MI compared to TAT. There was no significant difference in all-cause and cardiovascular death, stroke, and major adverse cardiovascular events.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on SYNTAX, which details all-cause mortality, stroke, MI or repeat revascularization 12 mo following PCI vs. CABG.

Table 12. Choice of Revascularization Procedure

	PCI	CABG
Advantages	Less invasive technique Decreased periprocedural morbidity and mortality Shorter periprocedural hospitalization	Greater ability to achieve complete revascularization Decreased need for repeated revascularization procedures
Factors favouring Revascularization Procedure	**Clinical characteristics** Severe comorbidity Advanced age/frailty/reduced life expectancy Restricted mobility and conditions that affect rehabilitation **Anatomical and technical aspects** MVD with SYNTAX score <23 Anatomy likely resulting in incomplete revascularization with CABG due to poor quality or missing conduits Severe chest deformation or scoliosis Sequelae of chest radiation Porcelain aort	**Clinical characteristics** Diabetes Reduced LV function (EF ≤35%) Contraindications to DAPT Recurrent diffuse in-stent restenosis **Anatomical and technical aspects** MVD with SYNTAX score ≥23 Anatomy likely resulting in incomplete revascularization with PCI Severely calcified coronary artery lesions limiting lesion expansion Need for concomitant interventions Ascending aortic pathology with indication for surgery Concomitant cardiac surgery

Note: Table reflects guidelines from the European Society of Cardiology that have been taught to Canadian cardiac surgery residents

Table 13. Conduits for CABG

Graft	Occlusion/Patency Rate	Considerations
Saphenous Vein Grafts (SVG)	At 10 yr: 50% occluded, 25% stenotic, 25% angiographically normal	Used to be commonly used, but arterial conduits have proven to be superior
Left Internal Thoracic/Mammary Artery (LITA/LIMA)	90-95% patency at 15 yr	Considered the standard conduit for CABG Excellent patency Almost always used to bypass LAD Improved event-free survival (angina, MI) Decreased late cardiac events
Right Internal Thoracic/Mammary Artery (RITA/RIMA)	Pedicled RIMA patency comparable to LIMA Lower rate of free RIMA patency	Used in bilateral ITA/IMA grafting Patients receiving bilateral ITAs/IMAs have less risk of recurrent angina, late MI, angioplasty
Radial Artery (free graft)	85-95% patency at 5 yr	Prone to severe vasospasm postoperatively due to vascular muscular wall
Right Gastroepiploic Artery	80-90% patency at 5 yr	Primarily used as an *in situ* graft to bypass the RCA Use limited because of the fragile quality of the artery, technical issues, increased operative time (laparotomy incision), and incisional discomfort with associated ileus
Complete Arterial Revascularization		For younger patients (<60 y/o) Preferred due to longer term graft patency
Redo Bypass Grafting		Indications for redo CABG: symptomatic patients (disabling angina) who have failed medical therapy, have stenotic vessels, have viable myocardium, have suitable distal targets Risk factors for redo CABG: poor control of HTN/hypercholesterolemia/smoking, normal LV, 1 or 2 vessel disease, no use of IMA/ITA in initial CABG, incomplete revascularization in initial CABG, young age Operative mortality 2-3 times higher than first operation 10% perioperative MI rate Reoperation undertaken only in symptomatic patients who have failed medical therapy and in whom angiography has documented progression of the disease Increased risk with redo-sternotomy secondary to adhesions which may result in laceration to aorta, RV, IMA/ITA, and other bypass grafts, uncontrollable hemorrhage, arterial bleeding and VFib, venous bleeding, or failure to arrest heart

Adapted from: Chikwe J, Beddow E, Glenville B. Cardiothoracic Surgery, 1st ed. Oxford, UK: Oxford UP. 2006.

Operative Issues

- LV function is an important determinant of outcome for all heart diseases
- patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, stress echo, positron emission tomography (PET) scanning, or MRI

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients with Three-vessel or Left Main Coronary Artery Disease
Lancet 2019;394:1325-34
Purpose: Report 10-yr all-cause mortality results as a 10-yr follow-up to the 2009 SYNTAX trial.
Methods: Adult patients with established left main CAD or three-vessel coronary disease were randomized to receive either PCI or CABG in a 1:1 ratio. Patients with a prior history of MI, PCI or CABG were excluded. The primary study endpoint was 10-yr all-cause mortality.
Results: 10-yr all-cause mortality rates were 28% and 24% for PCI- and CABG-treated patients, respectively (hazard ratio 1.19; 95% CI 0.99 to 1.43; P=0.066). In subgroup analysis, 10-yr all-cause mortality was 28% and 21% in PCI and CABG patients with three-vessel disease, respectively (hazard ratio 1.42; 95% CI 1.11 to 1.81). The same primary endpoint occurred in patients with left main coronary disease at a rate of 27% and 28% in PCI and CABG patients, respectively (hazard ratio 0.92; 0.69 to 1.22; P=0.023).
Conclusions: CABG provided a significant all-cause survival benefit in patients with three-vessel disease, compared to PCI in the same population. This effect was not observed in patients with left main CAD or in the pooled study sample.

Duration of Dual Antiplatelet Therapy Following Drug-eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with Longer Follow up
Catheter Cardiovasc. Interv. 2017; 90:31-7
Purpose: Conduct an updated meta-analysis to compare the efficacy and safety of short-term dual antiplatelet therapy (S-DAPT) vs. long-term DAPT (L-DAPT) in patients who underwent drug-eluting stent (DES) implantation.
Methods: RCTs comparing efficacy and/or safety outcomes for different DAPT durations after coronary DES implantation were searched in PubMed, CINAH, Cochrane CENTRAL, EMBASE, Scopus, and Web of Science. S-DAPT was defined as ≤12 mo duration of aspirin plus P2Y12 receptor inhibitor, while L-DAPT was defined as the same combination for >12 mo duration after DES implantation.
Results: 5 RCTs met all eligibility criteria and were included in the final meta-analysis. Outcomes of interest included all-cause mortality, cardiac mortality, myocardial infarction, stent thrombosis, target vessel revascularization, stroke, or major bleeding. Compared with L-DAPT, S-DAPT did not significantly increase the rate of stent thrombosis (OR 1.59; 95% CI 0.77 to 3.27). All-cause mortality, cardiac mortality, target vessel revascularization and stroke were also not significantly different between groups. However, S-DAPT was associated with an increased risk of MI (OR 1.48; 95% CI 1.04 to 2.10) and a lowered risk of major bleeding (OR 0.64; 95% CI 0.41 to 0.99).
Conclusions: In this meta-analysis with a longer follow-up time of ≥24 mo, S-DAPT compared to L-DAPT was associated with increased risk of MI but lower rates of major bleeding. No significant differences were found for all-cause mortality, cardiac mortality, stent thrombosis, target vessel revascularization, or stroke.

CABG and Antiplatelet Regimens

- refer to CCS guidelines 2018 update on antiplatelet therapy for more information
- prior to CABG, clopidogrel and ticagrelor should be discontinued for 5 d, and prasugrel for 7 d before surgery
- dual antiplatelet therapy should be continued for 12 mo in patients with ACS within 48-72 h after CABG
- ASA (81 mg) continued indefinitely (can be started 6 h after surgery)
- patients requiring CABG after PCI should continue their dual antiplatelet therapy as recommended in the post-PCI guidelines

Table 14. Risk Factors for CABG Mortality and Morbidity

Risk Factors for CABG Mortality	Risk Factors for CABG Postoperative Morbidity or Increased Length of Stay
Urgency of surgery (emergent or urgent)	Reoperation
Reoperation	Emergent procedure
Older age	Preoperative intra-aortic balloon pump (IABP)
Poor LV function (see below)	CHF
Female gender	CABG + valve surgery
Left main disease	Older age
Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, DM, cerebrovascular disease, and peripheral vascular disease	Renal dysfunction COPD DM Cerebrovascular disease

Note: risk factors are listed in decreasing order of significance

Procedural Complications

- CABG using CPB (see *Cardiopulmonary Bypass, C69*)
- stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
- immunosuppression
- deep sternal wound infection
- bleeding
- systemic inflammatory response leading to:
  - myocardial dysfunction
  - renal dysfunction
  - neurological injury
  - respiratory dysfunction
  - coagulopathies

OFF-PUMP CORONARY ARTERY BYPASS SURGERY

Procedure

- avoids the use of CPB by allowing surgeons to operate on a beating heart
  - stabilization devices (e.g. Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
  - procedure is safe and well tolerated by most patients; however, this surgery remains technically more demanding

Indications/Contraindications

- used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe PVD, severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g. Jehovah's Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- absolute contraindications: hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels, and calcified coronary vessels
- relative contraindications: cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

Outcomes

- OPCAB surgery decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
  - OPCAB has been associated with lower graft patency

See Landmark Cardiology and Cardiac Surgery Trials table for more information on ROOBY, which details the 5-year clinical outcomes in patients undergoing on-pump vs. off-pump CABG.

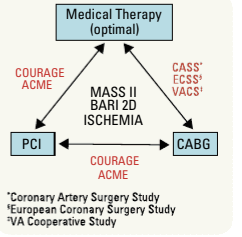


Figure 41. Clinical trials comparing strategies for stable CAD
Figure recreated with permission from Dr. Chris Overgaardn

Heart Failure

- see also CCS Heart Failure Guidelines 2021 for details (free mobile apps available on iOS and Android platforms in the CCS app stores) as well as the Canadian Cardiovascular Society (CCS) Heart Failure Guidelines Compendium available at CCS.ca

Congestive Heart Failure

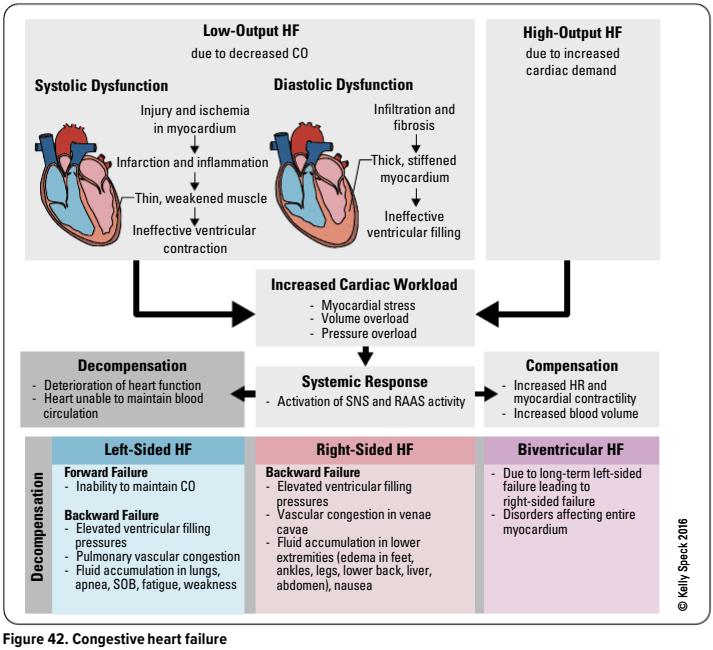

Low-Output HF
due to decreased CO
High-Output HF
due to increased cardiac demand
Systolic Dysfunction
Injury and ischemia in myocardium
Infarction and inflammation
Thin, weakened muscle
Ineffective ventricular contraction
Diastolic Dysfunction
Infiltration and fibrosis
Thick, stiffened myocardium
Ineffective ventricular filling
Increased Cardiac Workload
- Myocardial stress
- Volume overload
- Pressure overload
Decompensation
- Deterioration of heart function
- Heart unable to maintain blood circulation
Systemic Response
- Activation of SNS and RAAS activity
Compensation
- Increased HR and myocardial contractility
- Increased blood volume
Decompensation
Left-Sided HF
Forward Failure
- Inability to maintain CO
Backward Failure
- Elevated ventricular filling pressures
- Pulmonary vascular congestion
- Fluid accumulation in lungs, apnea, SOB, fatigue, weakness
Right-Sided HF
Backward Failure
- Elevated ventricular filling pressures
- Vascular congestion in venae cavae
- Fluid accumulation in lower extremities (edema in feet, ankles, legs, lower back, liver, abdomen), nausea
Biventricular HF
- Due to long-term left-sided failure leading to right-sided failure
- Disorders affecting entire myocardium
© Kelly Speck 2016

Figure 42. Congestive heart failure

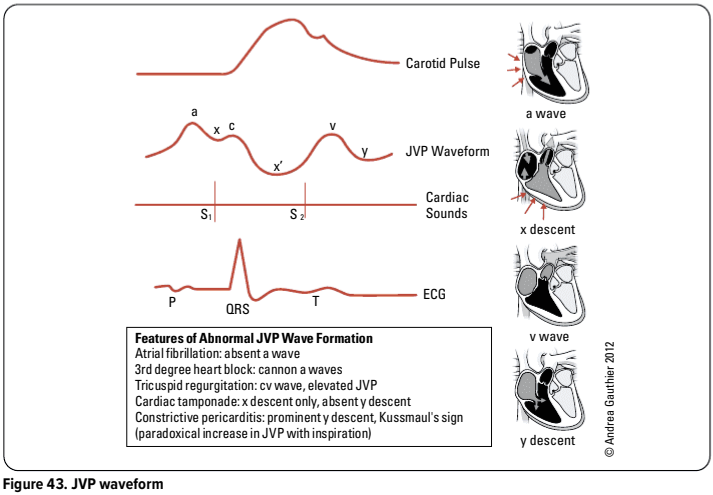


Figure 43. JVP waveform

Does this Dyspneic Patient in the Emergency Department have Congestive Heart Failure?
JAMA 2005;294:1944-1956

	LR + (95% CI*)	LR – (95% CI*)
Initial clinical judgment	4.4 (1.8-10.0)	0.45 (0.28-0.73)
PMHx		
HF	5.8 (4.1-8.0)	0.45 (0.38-0.53)
MI	3.1 (2.0-4.9)	0.69 (0.58-0.82)
CAD	1.8 (1.1-2.8)	0.68 (0.48-0.96)
Symptoms		
PND	2.6 (1.5-4.5)	0.7 (0.54-0.91)
Orthopnea	2.2 (1.2-3.9)	0.65 (0.45-0.92)
SOBOE	1.3 (1.2-1.4)	0.48 (0.35-0.67)
Physical Exam		
Third heart sound	11 (4.9-25)	0.88 (0.83-0.94)
Jugular venous distension	5.1 (3.2-7.9)	0.66 (0.57-0.77)
Rales	2.8 (1.9-4.1)	0.51 (0.37-0.70)
Lower extremity edema	2.3 (1.5-3.7)	0.64 (0.47-0.87)
Chest Radiograph		
Pulmonary venous congestion	12 (6.8-21)	0.48 (0.28-0.83)
Interstitial edema	12 (5.2-27)	0.68 (0.54-0.85)
Cardiomegaly	3.3 (2.4-4.7)	0.33 (0.23-0.48)
ECG		
AFib	3.8 (1.7-8.8)	0.79 (0.65-0.96)
Any abnormal finding	2.2 (1.6-3.1)	0.64 (0.47-0.88)

* CI = confidence interval

Dichotomies of HF
Forward vs. backward
Left-sided vs. right-sided
Systolic vs. diastolic dysfunction
Low output vs. high output

Use EF to Grade LV Dysfunction
Grade I (EF >60%) (Normal)
Grade II (EF = 40-59%)
Grade III (EF = 21-39%)
Grade IV (EF ≤20%)

Table 15. Signs and Symptoms of Left vs. Right HF

	Left Failure	Right Failure
Low CO (Forward)	Fatigue Syncope Systemic hypotension Cool extremities Slow capillary refill Peripheral cyanosis Pulsus alternans MR S3	Left failure symptoms if decreased RV output leads to LV underfilling TR S3 (right-sided)
Venous Congestion (Backward)	Dyspnea, orthopnea, PND Cough Crackles	Peripheral edema Elevated JVP with abdominojugular reflux ± Kussmaul's sign Hepatomegaly Pulsatile liver

Pathophysiology

- most common causes are ischemic heart disease, risk factors for CAD, LVH (HTN), valvular heart disease, and tachyarrhythmia
- myocardial insult causes pump dysfunction/impaired filling leading to myocardial remodeling and the following maladaptive changes:
  - pressure overload (e.g. AS or HTN) leads to compensatory hypertrophy (i.e. concentric remodeling) and eventually interstitial fibrosis
  - volume overload (e.g. aortic insufficiency) leads to dilatation (i.e. eccentric remodeling)
- remodeling results in decreased forward CO resulting in activation of the SNS and RAAS
- SNS causes tachycardia
- RAAS causes Na +and water retention to increase preload and afterload
- net result is increased cardiac demand leading to eventual decompensation

Heart Failure with Reduced Ejection Fraction (HFrEF: LVEF ≤40%)

- impaired myocardial contractile function → decreased LVEF and SV → decreased CO
- volume overload is the typical phenotype
- findings: apex beat displaced, S3, cardiothoracic ratio >0.5, decreased LVEF, LV dilatation
- causes
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - EtOH (and other toxins)
    - myocarditis
    - DCM (multiple causes see *Dilated Cardiomyopathy, C47*)
    - tachycardia-induced

Heart Failure with Mid-Range Ejection Fraction (HF-mrEF: LVEF 41-49%)

- includes patients who are recovering from HFrEF, declining from HFpEF, and transitioning to HFpEF
- characterization of HFmEF ongoing; guideline management does not currently exist

Heart Failure with Preserved Ejection Fraction (HFpEF: LVEF ≥50%)

- previously known as "diastolic HF"
- concentric remodelling with a "stiff" LV is the typical phenotype
- 50% of patients with HF have preserved EF; confers similar prognosis to HFrEF; more common in the elderly and females
- reduced LV compliance causes increased LV filling pressures, increased LA pressure/volume, and pulmonary congestion
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal EF
- causes
  - transient: ischemia (e.g. CAD, MI)
  - permanent: severe hypertrophy (HTN, AS, HCM), RCM (e.g. amyloid), MI

High-Output Heart Failure

- caused by demand for increased CO
- often exacerbates existing HF or decompensates a patient with other cardiac pathology
- DDx: anemia, thiamine deficiency (beriberi), hyperthyroidism, arteriovenous (A-V) fistula or left to right (L-R) shunting, Paget's disease, renal disease, hepatic disease

Precipitants of Symptomatic Exacerbations

- consider natural progression of disease vs. new precipitant
- always search for reversible cause

See Landmark Cardiology and Cardiac Surgery Trials table for more information on DAPA-HF which details the efficacy of SGLT2 inhibition in patients with HFrEF and without T2DM.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on PARADIGM-HF which details the survival outcomes of HFrEF patients treated with an ACEI or an angiotensin-neprilysin inhibitor.

Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure
J Am Coll Cardiol 2020; 75 (10) 1128–1141
Purpose: This study aimed to examine the impact of liraglutide on cardiovascular events and mortality among participants of the LEADER trial, based on their history of HF.
Methods: The LEADER trial included 9340 high-risk patients with type 2 diabetes who were assigned to receive liraglutide or placebo. The primary outcome was the occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Post hoc analyses were conducted based on baseline HF history (subgroups of presence vs. absence of HF).
Results: The effects of liraglutide compared to placebo on major adverse cardiovascular events were similar in patients with and without a history of HF (HR: 0.81 vs. 0.88, P=0.53). Liraglutide showed a reduction in deaths in both subgroups (HR:0.89 with HF; HR: 0.83 without HF; P=0.63). There was no increased risk of HF hospitalization with liraglutide, regardless of HF history (HR: 0.98 with HF; HR: 0.78 without HF; P=0.22). The effects of liraglutide on the composite outcome of HF hospitalization or cardiovascular death were consistent in patients with (HR: 0.92) and without a history of HF (HR: 0.77, P=0.19).
Conclusions: Liraglutide is recommended as a suitable treatment option for patients with type 2 diabetes, regardless of whether they have a history of New York Heart Association functional class I to III heart failure.

A Validated Clinical and Biochemical Score for the Diagnosis of Acute Heart Failure: the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Acute Heart Failure Score
Am Heart J 2006;151:48-54

Predictor	Possible Score
Age >75 yr	1
Orthopnea present	2
Lack of cough	1
Current loop diuretic use (before presentation)	1
Rales on lung exam	1
Lack of fever	2
Elevated NT-proBNP (>450 pg/mL if <50 yr, >900 pg/mL if >50 yr)	4
Interstitial edema on CXR	2
Total	/14
Likelihood of HF Low = 0-5 Intermediate = 6-8 High = 9-14	

- DDx can also be organized as follows:
  - new cardiac insult/disease: MI, arrhythmia, valvular disease, cardiotoxic chemotherapy
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection
  - medication non-compliance
  - dietary indiscretion (e.g. salt intake)
  - obstructive sleep apnea

Investigations
- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), blood urea nitrogen (BUN), Cr, fasting blood glucose, HbA1c, lipid profile, LFTs, serum TSH ± ferritin, BNP (>100 pg/mL), NT-ProBNP (>300 pg/ml), uric acid
- urinalysis
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchiolar-alveolar cuffing
- echo: systolic function (LVEF), diastolic function (E/A ratio, E/e'), cardiac dimensions, wall motion abnormalities, RV systolic pressure (from TR jet), valvular disease, pericardial effusion
- radionuclide angiography: LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

Additional Diagnostic Investigations
- cardiac catheterization
- cardiopulmonary exercise testing
- other tests (CMR, MPI, MUGA, CT scan)

Acute Treatment of Pulmonary Edema
- treat acute precipitating factors (e.g. ischemia, arrhythmias)
  - **L** Lasix® (furosemide) 40-500 mg IV
  - **M** morphine 2-4 mg IV: decreases anxiety and preload (venodilation)
  - **N** nitroglycerin: topical/IV/SL - use with caution in preload-dependent patients (e.g. right HF or RV infarction) as it may precipitate CV collapse
  - **O** oxygen: in hypoxemic patients
  - **P** positive airway pressure (continuous positive airway pressure (CPAP)/bilevel positive airway pressure (BiPAP)): decreases preload and need for ventilation when appropriate
  - **P** position: sit patient up with legs hanging down unless patient is hypotensive
- in ICU setting or failure of LMNOPP: other interventions may be necessary
  - nitroprusside IV
  - hydralazine PO
  - sympathomimetics
    - dopamine
      - low dose: selective renal vasodilation (high potency D1 agonist)
      - medium dose: inotropic support (medium potency β1 agonist)
      - high dose: increases SVR (low potency β1 agonist), which is undesirable
    - dobutamine
      - β1-selective agonist causing inotropy, tachycardia, hypotension (low dose) or HTN (high dose); most serious side effect is arrhythmia, especially AFib

      phosphodiesterase inhibitors (milrinone)
      - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
- consider pulmonary artery catheter to monitor PCWP if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
  - IABP - reduces afterload via systolic unloading and improves coronary perfusion via diastolic augmentation
  - LVAD/RVAD
  - cardiac transplant

Long-Term Management
- overwhelming majority of evidence-based management applies to HFrEF
- currently no proven pharmacologic therapies shown to reduce mortality in HFpEF; control risk factors for HFpEF (e.g. HTN)
- prevent fluid overload with appropriate diuretic strategies

Conservative Measures
- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease EtOH consumption, patient education, sodium, and fluid restriction
- multidisciplinary HF clinics: for management of individuals at higher risk, or with recent hospitalization

BNP is secreted by Vs due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into Vs, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP. The above scoring algorithm developed by Baggish et al. is commonly used. A score of <6 has a negative predictive value of 98%, while scores ≥6 had a sensitivity of 96% and specificity of 84% (P<0.001) for the diagnosis of acute HF

NYHA Functional Classification of HF
- **Class I**: ordinary physical activity does not cause symptoms of HF
- **Class II**: comfortable at rest; ordinary physical activity results in symptoms
- **Class III**: marked limitation of ordinary activity; less than ordinary physical activity results in symptoms
- **Class IV**: inability to carry out any physical activity without discomfort; symptoms may be present at rest

Five Most Common Causes of CHF

CAD (60-70%)

HTN

Idiopathic (often DCM)

Valvular (e.g. AS, AR, and MR)

EtOH (DCM)

Precipitants of HF

HEART FAILED

HTN (common)
Endocarditis/environment (e.g. heat wave)
Anemia
Rheumatic heart disease and other valvular disease
Thyrotoxicosis
Failure to take medications (very common)
Arrhythmia (common)
Infection/Ischemia/Infarction (common)
Lung problems (PE, pneumonia, COPD)
Endocrine (pheochromocytoma, hyperaldosteronism)
Dietary indiscretions (common)

The most common cause of right HF is left HF

Non-Pharmacological Management

- from 2021 CCS guidelines
- restrict salt intake to 2-3 g/d
- monitor daily weight for patients with HF, fluid retention, or congestion that is difficult to control with diuretics or renal dysfunction
- restrict daily fluid intake to approximately 2 L/d for patients with fluid retention or congestion that is difficult to control with diuretics
- cardiac rehabilitation: participation in a structured exercise program for NYHA class I-III after clinical status assessment to improve quality of life (HF-ACTION trial)

Pharmacological Therapy

- **ACEI/ARB:** RAAS blockade
  - ACEI: slows progression of LV dysfunction and improves survival
    - all symptomatic patients functional class II-IV
    - all asymptomatic patients with LVEF <40%
    - post-MI
  - angiotensin II receptor blockers
    - second-line to ACEI (if ACEI not tolerated), or as adjunct to ACEI if β-blockers not tolerated
    - combination of β-blockers with ACEI is not routinely recommended and should be used with caution as it may precipitate hyperkalemia, renal failure, and the need for dialysis (CHARM, ONTARGET)

- **antiarrhythmic drugs**: for use in CHF with arrhythmia
  - can use amiodarone, β-blocker, or digoxin

- **anticoagulants**: DOACs or vitamin K antagonist (warfarin) for prevention of thromboembolic events
  - prophylactic indications:
    - AFib
    - LV thrombus
    - Prior thromboembolic event

- **ARNI**: combination angiotensin receptor-neprilysin inhibitors - slows down progression of LV dysfunction and improves survival
  - RAAS inhibitor prevents volume overload and neprilysin inhibitor enhances effects of BNP
  - first line therapy or if switching from an ACEI or ARB among patients with residual NYHA II-IV symptoms and LVEF <40%

- **β-blockers**: slow progression and improve survival
  - β-adrenergic blocking agents blocks effects of epinephrine to reduce rate and force of myocardial contraction
  - indicated for class I-III with LVEF <40% and stable class IV patients
  - carvedilol improves survival in class IV HF (COMET)
  - caution: should be used cautiously; titrate slowly because may initially worsen CHF

- **diuretics**: management of fluid overload and symptom control (e.g. dyspnea and PND)
  - furosemide (40-500 mg QD) for potent diuresis
  - metolazone once weekly may be used with furosemide to increase diuresis if patient becomes refractory to furosemide
  - furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by β-blockers, ACEI, ARBs, and aldosterone antagonists

- **digoxin and cardiac glycosides**: increase myocardial contractility but decrease rate
  - improves symptoms and decreases hospitalizations; no effect on mortality
  - indications: patient in sinus rhythm and symptomatic on ACEI or CHF and AFib
  - caution: patients on digitalis glycosides may worsen if these are withdrawn

- **hydralazine plus isosorbide dinitrate**: combination antihypertensive and vasodilator
  - consider for symptom control and mortality benefit in Black patients with symptomatic HFrEF despite guideline-directed medical therapy (GDMT)
  - also consider for HFrEF patients with drug intolerance to ACEIs, ARBs, or ARNI

- **ivabradine**: selective inhibition of the If current
  - recommended for CV death and hospitalization prevention in patients with HFrEF and symptomatic despite:
    - treatment with appropriate doses of GDMT, resting HR >70 bpm, and in sinus rhythm
  - weaker level of evidence than either ARNI or SGLT2 inhibitor

- **mineralocorticoid receptor (aldosterone) antagonists**: spironolactone or eplerenone
  - mortality benefit in symptomatic HF and severely depressed EF
  - for symptomatic HF in patients already on ACEI, β-blocker, and loop diuretic
  - caution: potential for life threatening hyperkalemia
    - monitor K^+after initiation and avoid if Cr >220 μmol/L or K^+>5.2 mmol/L

Measuring NT-proBNP

BNP is secreted by Vs due to LV stretch and wall tension

Cardiomyocytes secrete BNP precursor that is cleaved into proBNP

After secretion into Vs, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP portion

	NT-proBNP levels (pg/mL)
Age	HF very likely
<50	>450
50-75	>900
>75	>1800

Limitations: Age, body habitus, renal function, PE

Features of HF on CXR

HERB-B

Heart enlargement (cardiothoracic ratio >0.50)

Pleural **E**ffusion

Re-distribution (alveolar edema)

Kerley **B** lines

Bronchiolar-alveolar cuffing

Patients on β-blocker therapy who have acute decompensated HF should continue β-blockers where possible (provided they are not in cardiogenic shock or in severe pulmonary edema)

CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure with Reduced Ejection Fraction

Can J Cardiol 2021;37:531-46

Management of HFrEF: It is recommended that, in the absence of contraindications, HFrEF patients be treated with combination therapy including 1 drug from each of the following categories: ARNI (or ACEI/ARB), β-blocker, mineralocorticoid receptor antagonist (MRA), and SGLT2 inhibitor. It is recommended that patients admitted with acute decompensated HFrEF be switched to an ARNI from an ACEI/ARB when stabilized. It is recommended that β-blockers be initiated as soon as possible after HF diagnosis, not waiting until hospital discharge to initiate treatment in stabilized patients. MRA treatment is recommended for patients with acute MI, LVEF <40%, and HF symptoms or DM to reduce CV mortality and hospitalization for CV events. SGLT2 inhibitors should be used in patients with HFrEF, with or without concomitant T2DM, to improve symptoms and reduce hospitalizations.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on DAPA-HF which details the efficacy of SGLT2 inhibition in patients with HFrEF and without T2DM.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on PARADIGM-HF which details the survival outcomes of HFrEF patients treated with an ACEI or an angiotensin-neprilysin inhibitor.

- **SGLT2 inhibitor**: empagliflozin, canagliflozin, dapagliflozin
  - recommended for treatment of patients with stable HFrEF, irrespective of T2DM
  - recommended in mild to moderate HFrEF with concomitant T2DM to improve symptoms and reduce mortality

HFrEF Management

1. ARNI (or if on ACEI/ARB substitute to ARNI)
2. β-blockers
3. MRA
4. SGLT2 inhibitor

HFpEF Management

1. ARB
2. Systolic/Diastolic Hypertension Management according to CHEP Guidelines (2017)
3. MRA (if serum K^+<5.0 mmol/L and eGFR >30 mL/min)

Surgical Management

- revascularization is the most frequently performed operation in HF patients with the aim to restore blood flow to hibernating myocardium (<10% operative mortality in some patient groups)
- mitral valve surgery for the treatment of MR secondary to ischemic LV dilation
- LV remodeling (Batista procedure - partial left ventriculectomy; Dor procedure - left ventricular restoration) improves ventricular function by reducing ventricular radial dimensions and thus decreasing wall tension via Laplace's law
- VADs (see *Cardiac Transplantation, C50*)
- heart transplantation (see *Cardiac Transplantation, C50*)

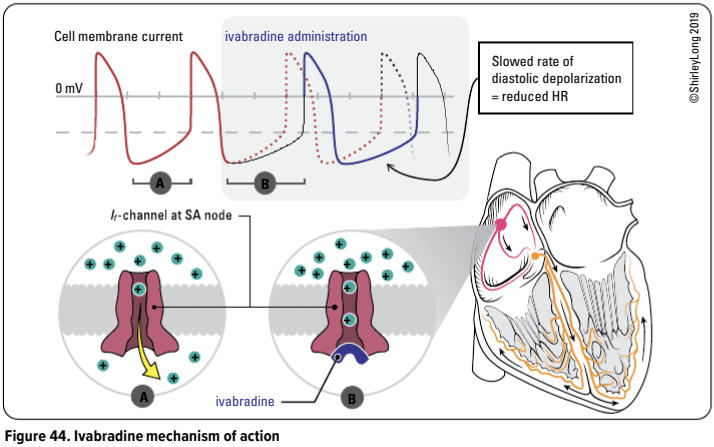


Figure 44. Ivabradine mechanism of action

Procedural Interventions

- resynchronization therapy: symptomatic improvement with CRT-P or CRT-D
  - consider if QRS >130 msec with LBBB morphology, LVEF <35%, and persistent symptoms despite OMT
  - greatest benefit likely with marked LV enlargement, MR, QRS >150 msec
  - CRT-P is indicated for patients eligible for resynchronization therapy but not ICD; if the patient is also eligible for an ICD the decision for CRT-D is individualized in accordance with overall goals of care
- ICD: mortality benefit in 1° prevention of SCD
  - consider if: prior MI, OMT, LVEF <30%, clinically stable
  - consider if: prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
- LVAD/RVAD (see *Ventricular Assist Devices, C52*)
- cardiac transplantation (see *Cardiac Transplantation, C50*)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see *Valvular Heart Disease, C54*)

Chronic Treatment of CHF

ACEI*

β-blockers*

± Mineralocorticoid receptor antagonists*

Diuretic

ARNI

± Inotrope

± Antiarrhythmic

± Anticoagulant

SGLT2 inhibitors

*Mortality benefit

SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis

EClinicalMedicine 2021;36:100933

Study: Systematic review and meta-analysis of placebo-controlled, randomized trials

Population: Patients with HF

Outcome: The primary endpoints were all-cause and cardiovascular mortality.

Results: In a meta-analysis of 15 trials with 20241 patients, SGLT2 inhibitors showed significant benefits. All-cause mortality was reduced by 14% (HR 0.86, 95% CI 0.79-0.94, P=0.0007) and cardiovascular mortality by 14% (HR 0.86, 95% CI 0.78-0.96, P=0.006). The composite outcome of cardiovascular mortality, heart failure hospitalizations, or urgent visits was significantly reduced in various subgroups.

Conclusions: SGLT2 inhibitors demonstrate significant reductions in both all-cause and cardiovascular mortality when compared to placebo in patients with heart failure.

Higher New York Heart Association Classes and Increased Mortality and Hospitalization in Patients with Heart Failure and Preserved Left Ventricular Function

Am Heart J 2006;151:444-450

Purpose: To establish the association between NYHA class and outcomes with HF and preserved systolic function.

Methods: Retrospective follow-up study (median 38.5 mo) of 988 patients with HF with EF >45%. Estimated risks of various outcomes using Cox proportional hazard models.

Results: Adjusted HR for all-cause mortality for NYHA class II, III, IV patients was 1.54, 2.56, and 8.46, respectively. Adjusted HR for all-cause hospitalization for NYHA class II, III, IV patients was 1.23, 1.71, and 3.4, respectively.

Conclusions: Higher NYHA classes were associated with poorer outcomes in patients with HF and preserved systolic function.

Proportions of NYHA I, II, III, and IV patients who died of all causes during the study were 14.3%.

NYHA	Proportion of All-Cause Hospitalization	Proportion of All-Cause Mortality
I	60.7%	14.3%
II	65.2%	21.3%
III	77.7%	35.9%
IV	75.0%	58.3%

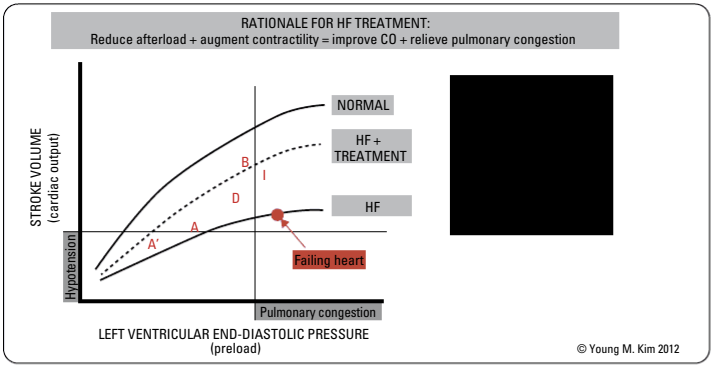


Figure 45. Effect of HF treatment on the Frank-Starling curve

Sleep-Disordered Breathing

- patients with CHF can have sleep disturbances; 40% of patients have central sleep apnea with Cheyne-Stokes breathing and 11% of patients have obstructive sleep apnea
- associated with a worse prognosis and greater LV dysfunction
- nasal CPAP may be effective to treat symptoms of sleep apnea with secondary benefits to cardiac function

Cardio-oncology

- cardiotoxicity of chemotherapeutic agents is a leading cause of long-term morbidity and mortality among cancer survivors
- dose-dependent LV systolic dysfunction with anthracyclines and potentially reversible decline in LVEF with trastuzumab
- evaluate CV risk factors and optimize treatment of pre-existing CV disease before, during, and after receiving cardiotoxic cancer therapy
- follow patient using same imaging modality and methods (e.g. echo with contrast, echocardiographic global longitudinal strain (GLS), 3 dimensional echo, or multiple-gated acquisition (MUGA) scan) to assess LV function before, during, and upon completion of chemotherapy
- recommended that clinical HF or an asymptomatic decline in LVEF (>10% decrease in LVEF from baseline or LVEF <53%) during or after treatment is managed according to CCS guidelines

Myocardial Disease

Definition of Cardiomyopathy

- intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
  - results in both morphologic and functional abnormalities
- functional classification: dilated, hypertrophic, or restrictive
- LV dysfunction secondary to MI, often termed "ischemic cardiomyopathy," is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD

Cardiomyopathy

HARD
Hypertrophic cardiomyopathy (HCM)
Arrhythmogenic right ventricular cardiomyopathy
Restrictive cardiomyopathy (RCM)
Dilated cardiomyopathy (DCM)

Table 16. Comparison of Cardiomyopathies, Secondary Causes, and Consequent HF Phenotypes

Heart Failure Reduced Ejection Fraction (HFrEF)		Heart Failure Preserved Ejection Fraction (HFpEF)		
Dilated Cardiomyopathy (DCM)	**Secondary Causes**	**Hypertrophic Cardiomyopathy (HCM)**	**Restrictive Cardiomyopathy (RCM)**	**Secondary Causes**
Idiopathic, infectious (e.g. myocarditis), EtOH, familial, collagen vascular disease	CAD, MI, DM, valvular (e.g. AR, MR)	Genetic disorder affecting cardiac sarcomeres (most common cause of SCD in young athletes)	Amyloidosis, sarcoidosis, scleroderma, hemochromatosis, Fabry's, Pompe's Disease, Loeffler's	HTN, DM, valvular (e.g. AS), post-MI, transiently by ischemia

Myocarditis

Definition
- inflammatory process involving the myocardium ranging from acute to chronic
- important cause of DCM
- spectrum of severity ranging from non-specific symptoms such as fatigue to cardiogenic shock

Etiology
- idiopathic
- infectious
  - viral (most common overall cause): coxsackie A and B, parvovirus B19, adenoviruses, influenza, echovirus, poliovirus, HIV, mumps, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  - bacterial: *S. aureus, Streptococcus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia*
  - fungi
    - spirochetal (Lyme disease *Borrelia burgdorferi*)
  - Chagas disease (*Trypanosoma cruzi*), *Toxoplasma gondii*
- toxic: catecholamines, chemotherapy, cocaine
- hypersensitivity/eosinophilic: drugs (e.g. antibiotics, diuretics, lithium, clozapine), insect/snake bites, mRNA vaccines (rare)
- systemic diseases: collagen vascular diseases (e.g. SLE, rheumatoid arthritis), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

Signs and Symptoms
- constitutional symptoms
- acute CHF: dyspnea, tachycardia, elevated JVP
- cardiogenic shock
- chest pain: due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- presyncope/syncope/sudden death

Investigations
- ECG: non-specific ST-T changes and/or conduction defects (used for initial screening and risk stratification)
  - echocardiography: lack of cardiac dilation and increased thickness of septum (fulminant myocarditis), spherical ventricle that remodels to elliptical after some months (acute myocarditis)
- blood work
  - increased creatine kinase (CK), cardiac troponins (cTnI and cTnT), NT-proBNP (if LV dysfunction occurs), LDH, and AST with acute myocardial necrosis ± increased WBC, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody test (ANA), rheumatoid factor, complement levels
  - blood culture, viral titres, and cold agglutinins for Mycoplasma
- CXR: enlarged cardiac silhouette
- TTE: systolic dysfunction (dilated, hypokinetic chambers, segmental wall motion abnormalities) and/or diastolic dysfunction
- CMR: functional and morphological abnormalities as well as tissue pathology (gadolinium enhancement)
- endomyocardial biopsy: only done in certain clinical scenarios (e.g. on inotropic and/or mechanical circulatory support)
- coronary angiography: to exclude ischemic heart disease

Management
- supportive care
- mechanical circulatory support and inotropic support if cardiogenic shock
- restrict physical activity during early recovery
- treat CHF per current HF guidelines
  - guideline-directed medical therapy
  - advanced therapies such as ventricular assist and transplantation
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible

Prognosis
- often unrecognized and may be self-limited
- myocarditis treatment trial showed 5 yr mortality between 25-50%
- giant cell myocarditis, although rare, can present with fulminant CHF and be rapidly fatal, with 5 yr mortality >80%
- sudden death in young adults
- may progress to DCM

Dilated Cardiomyopathy

Major Risks Factors for DCM
FMHx, EtOH, cocaine,

Abnormal Labs in DCM
- High BNP
- High Cr
- High LFTs
- Low bicarbonate
- Low Na+

Definition
- unexplained dilation and impaired systolic function of one or both ventricles
- if present, comorbid CAD is unable to fully account for extent of dysfunction observed

Etiology
- familial/genetic ~60%
- EtOH ~20-30%
- myocarditis
- infectious: viral (coxsackie B, HIV, SARS-CoV-2), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
- collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
- idiopathic (presumed viral or idiopathic)
- uncontrolled tachycardia (e.g. persistent, rapid AFib)
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), anti-retrovirals, chloroquine, clozapine, TCA
- radiation

Signs and Symptoms
- may present as:
  - systolic HF
  - systemic or pulmonary emboli
  - arrhythmias
  - sudden death (major cause of mortality due to fatal arrhythmia)

Investigations
- blood work: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, total iron binding capacity (TIBC)
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (e.g. non-sustained VT)
- CXR: global cardiomegaly (i.e. globular heart), signs of CHF, pleural effusion
- echo: systolic dysfunction (chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi)
- cardiac MRI: myocardial fibrosis
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- coronary angiography: in select patients to exclude ischemic heart disease

Management
- treat underlying disease: e.g. abstinence from EtOH
- treat CHF as per current guidelines (see *Heart Failure, C40*)
  - includes medical management and devices (ICD and CRT)
- advanced therapies considered for medication-refractory disease
  - e.g. LVAD, transplant, and volume reduction surgery
- thromboembolism prophylaxis: anticoagulation with warfarin
  - indicated for: AFib, history of thromboembolism or documented thrombus
- treat symptomatic or serious arrhythmias
- immunize against influenza and S. pneumoniae
- indication to screen first-degree relatives when unclear etiology

Prognosis
- depends on etiology, often parallels prognosis of systolic HF
- better with reversible underlying cause; worst with infiltrative diseases, HIV, drug-induced
- early reverse remodelling with optimal HF management (i.e. medications and devices) improves prognosis
- myocardial fibrosis increases SCD risk
- cause of death usually CHF (due to pump failure) or sudden death secondary to ventricular arrhythmias
- systemic emboli are significant source of morbidity
- 20% mortality in first yr, 10% per year thereafter

Hypertrophic Cardiomyopathy

- see 2020 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy for details

Definition

- unexplained left ventricular hypertrophy (LVH)
- LVH can occur in any distribution
  - asymmetric septal hypertrophy is most common
- systolic anterior motion of mitral valve and hyperdynamic LV are common but non-diagnostic

Etiology

- cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins
  - >400 mutations associated with autosomal dominant inheritance, incomplete penetrance, variable age of onset
  - 70% of pathogenic variants occur within 2 genes: β-myosin heavy chain 7 (MYH7) and myosin-binding protein C3 (MYBPC3)
- prevalence of 1 in 500 to 1 in 1000 in general population
  - equally prevalent in men and women although women are diagnosed less often
- generally presents in early adulthood

Pathophysiology

- histopathologic features include myocyte disarray, myocyte hypertrophy, dysplastic arterioles and interstitial fibrosis
- dynamic obstruction of LVOT (LVOTO) due to both septal hypertrophy and systolic anterior motion (SAM) of mitral leaflets
- diastolic dysfunction due to LVH, ischemia, and interstitial fibrosis
- myocardial ischemia due to supply-demand mismatch
- autonomic dysfunction, inappropriate vasodilation during exercise, and abnormal HR recovery

Hemodynamic Classification

- HOCM (hypertrophic obstructive cardiomyopathy): defined as peak LVOT gradient of at least 30 mmHg either at rest or with provocation
  - peak LVOT gradient of at least 50 mmHg at rest or provoked is the typical threshold for considering invasive septal reduction in patients with insufficient response to medical management
- non-obstructive HCM (one-third): no LVOT obstruction

Signs and Symptoms

- clinical manifestations: asymptomatic (common, therefore screening is important), SOBOE, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
- pulses: rapid upstroke, "spike and dome" pattern in carotid pulse (in HCM with outflow tract obstruction)
- precordial palpation: PMI localized, sustained, double impulse, 'triple ripple' (triple apical impulse in HOCM), LV lift
- precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLSB or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOTO as compared to AS); often with pansystolic murmur due to MR

Investigations

- 3-generation family history
  - first-degree relatives receive directed cascade genetic testing and routine TTE and ECG screening
  - first-degree relatives are screened every 1-3 yr as children and every 3-5 yr as adults provided they are asymptomatic and initial assessment is negative
- TTE for initial diagnosis, monitoring every 1-2 yr and evaluating clinical concerns
  - for patients not meeting LVOTO criteria (LVOT gradient of at least 50 mmHg) at rest, a provocative maneuver and/or exercise stress test is performed to assess for dynamic LVOTO development
- TEE for preoperative planning of septal reduction, assessment of MR etiology, SAM, and LVOTO
- cardiac MRI to clarify inconclusive echocardiogram results or determine method of septal reduction
- ECG/holter monitor for initial workup, regular follow-up, and assessment of SCD risk
  - LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- cardiac catheterization (only when patient being considered for invasive therapy)
- genetic studies to clarify uncertain diagnoses and facilitate screening of family members

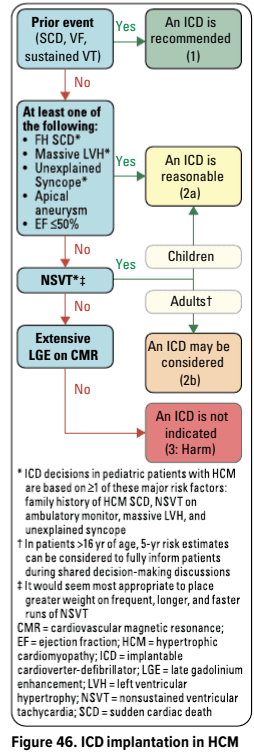

Prior event (SCD, VF, sustained VT)
Yes
An ICD is recommended (1)
No
At least one of the following:
• FH SCD*
• Massive LVH*
• Unexplained Syncope*
• Apical aneurysm
• EF ≤50%
Yes
An ICD is reasonable (2a)
No
NSVT*‡
Yes
Children
Adults†
No
Extensive LGE on CMR
An ICD may be considered (2b)
No
An ICD is not indicated (3: Harm)
* ICD decisions in pediatric patients with HCM are based on ≥1 of these major risk factors: family history of HCM SCD, NSVT on ambulatory monitor, massive LVH, and unexplained syncope
† In patients >16 yr of age, 5-yr risk estimates can be considered to fully inform patients during shared decision-making discussions
‡ It would seem most appropriate to place greater weight on frequent, longer, and faster runs of NSVT
CMR = cardiovascular magnetic resonance; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death

Figure 46. ICD implantation in HCM

Management
- avoid factors which increase obstruction (e.g. volume depletion)
  - avoidance of high-intensity competitive sports unless exceptional circumstances
  - mild-to-moderate-intensity exercise is safe
- treatment of HOCM
  - medical agents: β-blockers, verapamil or diltiazem (started only in monitored settings), disopyramide, phenylephrine (in setting of cardiogenic shock), mavacamten
  - avoid digoxin and vasodilators (e.g. nitrates, dihydropyridine calcium channel blockers, and ACEi/ARB) as they are inotropic and afterload reducing, respectively
- patients with HOCM and drug-refractory symptoms require septal reduction therapy at experienced centres
  - surgical myectomy
  - alcohol septal ablation - percutaneous intervention that ablates the hypertrophic septum with 100% ethanol via the septal artery
  - dual chamber pacing (rarely done)
- treatment of non-obstructive HCM
  - symptomatic: β-blockers or non-dihydropyridine calcium channel blockers and diuretics if refractory symptoms
- comorbid atrial fibrillation: direct oral anticoagulant or warfarin regardless of CHA2DS2-VASc score
- consequent systolic dysfunction: consider candidacy for transplant
- treatment of patients at high-risk of sudden death: ICD (see *Figure 46, ICD implantation in HCM, C48*)
  - history of survived cardiac arrest/sustained VT
  - FMHx of premature sudden death
  - other factors associated with increased risk of SCD
    - syncope (presumed to be arrhythmic in origin)
    - LVEF <50%
    - LV apical aneurysm
    - non-sustained VT on ambulatory monitoring
    - marked LVH (maximum wall thickness ≥30 mm)

Prognosis
- life expectancy may or may not be reduced
  - the majority of those with HCM do not experience severe symptoms or require aggressive treatments
- potential complications: AFib, stroke, CHF (diastolic and systolic), VT, SCD (1% risk/yr; most common cause of SCD in young athletes)

Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM): A Randomized, Double Blind, Placebo-Controlled, Phase 3 Trial
The Lancet 2020 Sep 12;396(10253):759-69.
Purpose: Assess the safety and efficacy of mavacamten, a cardiac myosin inhibitor, in symptomatic HOCM.
Methods: Patients with HOCM (LVOT>50mmHg, NYHA II-III) from 68 clinical centers in 13 countries were randomized to mavacamten or placebo for 30 wk. The primary endpoint was a >1.5mL/kg/min increase in peak O2 consumption and at least one NYHA class reduction, or >3.0mL/kg/min increase in peak O2 consumption with no NYHA class reduction.
Results: 45 (37%) of 123 patients on mavacamten vs. 22 (17%) of 128 on placebo met the primary endpoint. Patients on mavacamten had greater reductions in post-exercise LVOT gradient and greater increase in peak O2 consumption. 34% more patients in the mavacamten group improved by at least 1 NYHA class. Safety and tolerability were comparable to placebo.
Conclusion: Mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with HOCM.

Restrictive Cardiomyopathy

Definition
- impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)
- biatrial enlargement is often present despite normal AV valve functioning

Etiology
- most commonly: amyloidosis, sarcoidosis, and hemochromatosis
- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis, diabetic cardiomyopathy
- storage diseases: hemochromatosis, Fabry's disease, Gaucher's disease, glycogen storage diseases
- endomyocardial
  - endomyocardial fibrosis (late presentation), Loeffler's endocarditis, or eosinophilic endomyocardial disease
  - radiation heart disease
  - carcinoid syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)

RCM vs. Constrictive Pericarditis
Present similarly but constrictive pericarditis is treatable with surgery

RCM	Constrictive Pericarditis
Family history	Prior surgical history in some cases
No pulsus paradoxus	Pulsus paradoxus may be present
Systolic murmurs	Pericardial rub
Lvh	No lvh
Normal pericardium (intracardiac pathology)	Pericardial calcification and pericardial thickening
Myo- and endocardial later gadolinium enhancement (lge)	Pericardial late gadolinium enhancement (lge)
Elevated bnp	Reduced bnp

Clinical Manifestations
- CHF (usually with preserved LV systolic function), arrhythmias
- elevated JVP with prominent x and y descents, Kussmaul's sign
- S3, S4, MR, TR
- thromboembolic events

Investigations
- ECG: low voltage, non-specific, diffuse ST-T wave changes ± non-ischemic Q waves
- CXR: mild cardiomegaly due to biatrial enlargement
- echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
- cardiac MRI: assessment of myocardial fibrosis, determination of etiology, and exclusion of constrictive pericarditis
- cardiac catheterization: increased end-diastolic ventricular pressures
- endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

Management
- exclude constrictive pericarditis
- control HR, anticoagulate if AFib
- treat underlying disease: (e.g. cardiac amyloidosis, cardiac sarcoidosis, hemochromatosis)
- supportive care and treatment for CHF, arrhythmias, and prevention of SCD when indicated
  - judicious use of diuretics (excess volume reduction reduces filling pressures versus pathologic requirements triggering hypoperfusion)
- cardiac transplant: might be considered for CHF refractory to medical therapy

Prognosis
- depends on etiology

Key Investigations

Echo: may show respiratory variation in blood flow in constrictive pericarditis

CT: may show very thickened pericardium and calcification in constrictive pericarditis

MRI: best modality to directly visualize pericardium and myocardium

Left Ventricular Noncompaction Cardiomyopathy

Definition
- failure of LV compaction leading to endomyocardial trabeculations that increase in number and prominence
- characterized by abnormal trabeculations in the LV, most frequently at the apex

Etiology
- genetics are incompletely understood
- mutations have been mainly observed in genes coding sarcomeric, cytoskeletal, and mitochondrial proteins
- can occur in healthy individuals (e.g. athletes and pregnancy) as well as concomitantly with congenital heart diseases and other cardiomyopathies (i.e. HCM, RCM, DCM, ARVC)
- can be reversible

Clinical Manifestations
- if occurring in absence of concomitant cardiomyopathy and congenital heart disease, LV non-compaction can be benign
- symptoms range from SOBOE to rest symptoms
  - many patients are asymptomatic
- ventricular arrhythmias or complete AV block (presents as syncope and sudden death)
- thromboembolic events
  - more likely when systolic dysfunction and LV dilatation are present

Investigations
- directed by primary pathology when LV non-compaction is comorbid with congenital disease or other cardiomyopathies
- TTE and cardiac MRI
  - most common diagnostic method is the ratio of the thickness of the non-compacted layer to that of the compacted layer (greater than 2:1 at the end of diastole)
- role of routine genetic screening remains in question
  - typically performed in the setting of LV non-compaction with comorbid cardiomyopathy

Management
- at-risk first-degree relatives are recommended to undergo screening
- therapy is largely driven by concomitant myocardial dysfunction, arrhythmias, and congenital heart disease
- ICD is an option if patients have syncope, documented VT, or LV systolic dysfunction
- antiplatelets or systemic anticoagulation should be considered in adults, especially when the LV or atria are dilated

Prognosis
- dependent on LV function and presence of comorbid conditions (e.g. congenital heart disease and cardiomyopathy)

Cardiac Transplantation

- treatment for end-stage heart failure
- median survival is 12.5 yr, extending to 14.8 yr among 1-year survivors
- matching is according to blood type, body size and weight (should be within 25%), HLA tissue matching, and geographical considerations (to minimize ischemic time)

Indications for Surgery
- severe cardiac disability despite maximal medical therapy (e.g. recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 mL/kg/min in absence of β-blocker) with a life expectancy of 12-18 mo
- symptomatic cardiac ischemia refractory to conventional treatment (e.g. unstable angina not amenable to CABG or PCI with LVEF <20-25%; recurrent, symptomatic ventricular arrhythmias)

- high-risk HFSS
  - HFSS is an algorithm that incorporates the patient's HR, serum sodium, ischemic cardiomyopathy, LVEF, peak myocardial oxygen consumption, MAP, interventricular conduction delay
  - patients with medium-risk (HFSS 7.2-8.1, 73% 1-yr survival) and high-risk (HFSS <7.2, 43% 1-yr survival) benefit from cardiac transplant
- cardiogenic shock requiring IV inotropic agents or mechanical circulatory support to sustain organ perfusion
- exclusion of all surgical alternatives to cardiac transplantation

Absolute Contraindications
- active alcohol use disorder or substance use disorder
- actively smoking
- coagulopathy
- incurable malignancy
- irreversible major organ disease
- irreversible pulmonary HTN (i.e. >5 Wood units, transpulmonary gradient <18 mmHg, or systolic pulmonary artery pressure >60 mmHg)
- major systemic illness
- mental illness or other cognitive factors likely to affect ability to adhere to post-transplant regimens
- repeated non-adherence to medications
- severe COPD (i.e. FEV_1 <1L)
- severe symptomatic cerebrovascular disease

Relative Contraindications
- active systemic infection
- acute PUD
- age >70 yr
- DM with end-organ disease
- lack of family/social support
- obesity (>35 kg/m^2)
- significant symptomatic carotid disease or PVD

Prerequisites
- psychosocial stability
- medically compliant and motivated

Complications
- rejection
  - declining incidence with improved post-transplant immunosuppression regimens: <13% experience an episode that needs to be treated and <5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
  - risk of acute rejection is greatest during the first 3 mo after transplant
  - hyperacute rejection (minutes to hours after transplant) due to ABO mismatch, acute rejection (days to months after transplant), or chronic rejection (years after transplant)
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
  - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft vasculopathy
  - approximately 50% develop graft vasculopathy within 10 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
  - second most common cause of late death following transplantation
  - cutaneous neoplasms most common, followed by non-Hodgkin lymphoma and lung cancer
- medication side effects
  - immunosuppressives (e.g. prednisone, cyclosporine nephrotoxicity, tacrolimus) may have nephrotoxic effects
- cardiac denervation
  - as the donor heart is completely denervated, it does not receive parasympathetic vagal stimulation or intrinsic postganglionic sympathetic stimulation so it will not respond to anticholinergics like atropine
- RV dysfunction
  - RV dysfunction with TR, particularly in patients with preoperative pulmonary HTN, due to myocardial dysfunction caused by long ischemic time and/or reperfusion injury
  - requires aggressive management for treatment using agents that dilate the pulmonary vasculature or, rarely, RVAD support

Effects of Donor Pre-Treatment with Dopamine on Survival after Heart Transplantation: A Cohort Study of Heart Transplant Recipients Nested in a Randomized Controlled Multicentre Trial
J Am Coll Cardiol 2010;58:1768-1777
Treatment of brain-dead donors with dopamine of 4 μg/kg/min will not harm cardiac allografts but appears to improve the clinical course of the heart allograft recipient.

Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure
NEJM 2001;345:1435-1443
Increased survival of 23% vs. 8% with LVAD vs. medical management of HF after 2 yr.
Heartmate VAD has a biologic surface and, therefore, does not require long-term anticoagulation but confers a higher risk of infection.

Canadian Cardiovascular Society Focused Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive: Fitness following Left Ventricular Assist Device Implantation
Can J Cardiol 2012;28:137-140
Patients with a continuous flow LVAD (NYHA class I-III) who are stable 2 mo post-LVAD implantation qualify for private driving (only) and are disqualified from commercial driving.

Canadian Cardiovascular Society/ Canadian Cardiac Transplant Network Position Statement on Heart Transplantation: Patient Eligibility, Selection, and Post-Transplantation Care
Can J Cardiol 2020;36:335-56
Selection Criteria: Cardiac transplantation is recommended for consideration in HF patients ≤70 yr old. For all patients being considered, an assessment of frailty with a validated tool is recommended. Caution is recommended for patients with BMI >35. LVAD implantation is recommended for eligible patients with pulmonary hypertension on right heart catheterization. Finally, cardiac transplantation is not recommended for patients who show repeated nonadherence to medications, alcohol or illicit drug use, mental illness, and/or cognitive concerns that will render patients unlikely to adhere to post-transplantation regimens.

Ventricular Assist Devices

- work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD), or both ventricles (BiVAD); typical circuit is comprised of a pump, an outflow graft, and a driveline to connect to an external power source and controller (see *Figure 48*)
- indications:
  - bridge to transplantation, bridge to decision (for transplant), or long-term permanent therapy ("destination therapy")
  - postoperative mechanical support when unable to separate from CPB despite inotropic and IABP support
    - IABP is a catheter-based device inserted into the femoral artery and advanced to the descending aorta that decreases afterload, thus myocardial O_2 demand and increases blood flow to coronary arteries
    - inflation of the balloon occurs during diastole to increase ascending aorta and coronary artery perfusion pressure; deflation occurs at systole to reduce intra-aortic pressure thus reducing afterload
  - cardiogenic shock

Extracorporeal Membrane Oxygenation

- circuit includes: centrifugal pump, membrane oxygenator, venous and arterial cannulas (see *Figure 47*)
- venoatrial (VA) ECMO is treatment for cardiogenic shock due to broad availability, technical simplicity, and rapid deployment
- outcomes for ECMO poor with 35% survival
- indications: postcardiotomy shock, allograft failure, fulminant myocarditis, decompensated HF
- extracorporeal life support through ECMO use is an effective method of resuscitation in moribund patients

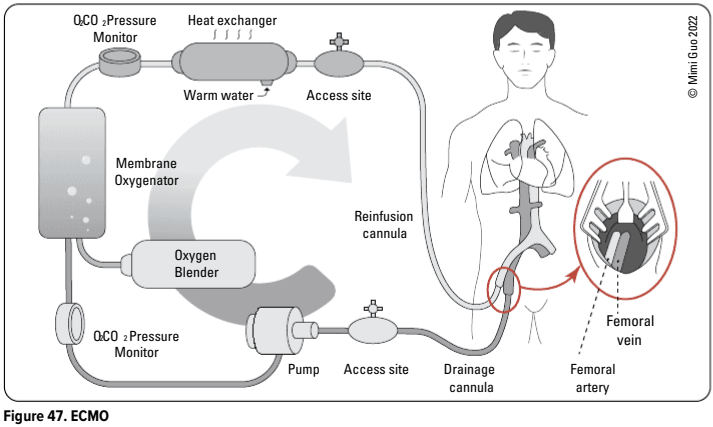


Figure 47. ECMO

Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device
NEJM 2009;361:2241-51
Purpose: Assess quality of life in patients with advanced HF treated with implanted pulsatile-flow LVAD or new continuous-flow devices.
Methods: Patients with advanced medically-refractory HF were randomized (in a 2:1 ratio) to implantation of a continuous-flow LVAD or a pulsatile-flow LVAD. Quality-of-life tests and 6-min walk test data were collected at baseline, 1 month, 3 mo, 6 mo, then every 6 mo until study completion. The primary endpoint was a composite of 2-yr survival free of disabling stroke (Rankin score >3), or device reoperation for replacement.
Results: 86% of patients with the continuous-flow device and 76% of patients with the pulsatile-flow device were discharged from the hospital with the device in-place. The primary endpoint was achieved in 46% of patients implanted with the continuous-flow device, compared to 11% with the pulsatile-flow device (hazard ratio 0.38; 95% CI 0.27 to 0.54; P<0.001). The Kaplan-Meier estimates of survival revealed significantly better outcomes for patients with the continuous-flow devices compared with the pulsatile-flow device (RR 0.54; 95% CI 0.34 to 0.86; P=0.008).
Conclusions: Implantation of a continuous-flow device, compared to a pulsatile-flow device improved stroke-free survival and quality of life in patients with advanced medically-refractory HF.

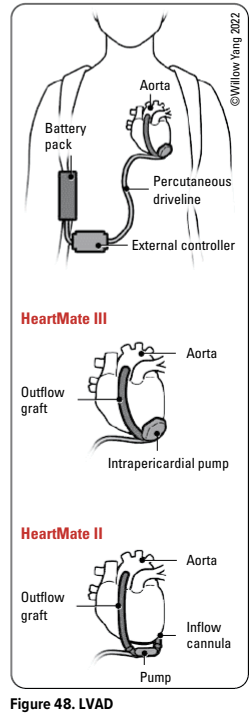


Figure 48. LVAD

Cardiac Tumours

Incidence

- cardiac tumours are more commonly derived from metastases than primary tumours
  - primary cardiac tumours have an estimated incidence of 1-30 in 100000 people per year
  - metastatic involvement of the heart is much more common and is present in 10-20% of autopsies of patients who die from cancer

Diagnosis

- TTE, TEE, MRI, PET and/or CT scan can be used to detect cardiac tumours
  - transvenous and open biopsy offer definitive diagnosis when required
- once detected, CT or PET scans screen for distant metastasis while cardiac MRI helps determine suitability for surgery
  - coronary angiography determines presence of concomitant CAD and neoplastic involvement of coronary vasculature

Physiological Consequences of Cardiac Tumours

- systemic or pulmonic embolization
- symptoms of HF due to obstruction of circulation
- regurgitation due to interference with heart valves
- myocardial invasion causing impaired left ventricular function, arrhythmias, heart block, or pericardial effusion
- constitutional or systemic symptoms

Subtypes of Cardiac Tumours by Location

- right atrial tumours
  - may obstruct blood flow and present with symptoms similar to those of TS and right HF
  - fragments from right atrial tumours may cause pulmonary emboli
  - tumours affecting the AV node can cause heart block
  - myxomas are one of the most common
- right ventricular tumours
  - can induce right-sided HF by interfering with filling or outflow from the RV
  - may obstruct blood flow or beget TR and, as a result, simulate mitral valve disease and produce HF or secondary pulmonary HTN
- left atrial tumours
  - may release tumour fragments or thrombi into the systemic circulation
  - myxomas are one of the most common
- left ventricular tumours
  - intramural left ventricular tumours may induce arrhythmias or conduction defects
  - intracavitary tumours can present with systemic embolization or outflow obstruction
  - may ultimately result in left ventricular failure
- valvular tumours
  - papillary fibroelastomas are most common, equal incidence at AV and semilunar valves
  - asymptomatic until sentinel events such as distal embolization and coronary ostial obstruction
  - resection and repair of the valvular tissue is preferred over valve replacement
- pericardial tumours
  - includes lipomas and metastatic tumours
  - external compression of the heart as a result of both mass effect and propensity to generate pericardial effusions

Subtypes of Cardiac Tumours by Histopathology

- benign tumours
  - roughly 75% of cardiac tumours are benign
  - myxomas make up the majority of benign cardiac tumours and they most commonly arise in the LA
  - in patients over age 16, the three most common primary tumours are myxomas (50%), lipomatous tumours (21%), and papillary fibroelastomas (16%)
  - in patients under age 16, the four most common tumours are rhabdomyomas (55%), teratomas (16%), fibromas (10%), and myxomas (10%)
  - myxomas should be surgically resected to minimize the risk of cardiovascular complications, including embolization
- primary malignant cardiac tumours
  - sarcomas are the most common form of primary malignant cardiac tumours (75%)
  - these tumours progress rapidly and can infiltrate the myocardium, obstruct circulation, and release metastatic cells
  - prognosis dictated by anatomic location as opposed to histopathology
  - right-sided tumours are more invasive and metastasize earlier than left-sided ones
  - although the recommended treatment strategy is surgical resection when possible, these tumours are likely to recur
  - a combination of chemotherapy and surgical resection for primary cardiac sarcomas prolongs survival as compared with either surgery or chemotherapy alone
- metastatic involvement of the heart
  - metastatic cancer cells may reach the heart through hematogenous spread, direct invasion, or tumour growth through the venae cavae into the RA
  - incidence is highest in external layers of heart and reduced toward luminal layers, reflecting seeding through the coronary arteries and direct extension of adjacent thoracic tumours
  - when a cancer patient develops cardiovascular symptoms, cardiac or pericardial metastases should be suspected
  - although most metastases are asymptomatic, the most common symptom is pericardial effusion with or without tamponade

Valvular Heart Disease

- see the 2020 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Management of Patients with Valvular Heart disease and the 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guidelines for the Management of Patients with Valvular Heart disease for details

Infective Endocarditis

- see Infectious Diseases, ID15
- American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  - only for patients with:
    - prosthetic valve material
    - past history of IE
    - cyanotic CHD
    - cardiac transplant recipients who develop valvulopathy
  - only for the following procedures:
    - dental
    - respiratory tract
    - procedures on infected skin/skin structures/MSK structures
    - not GI/GU procedures specifically

Rheumatic Fever

- see Pediatrics, P65

Prognosis

- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
- onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
- mitral valve most commonly affected

Valve Repair and Valve Replacement

- indication for valve surgery depends on the severity of the pathology; typically recommended when medical management has failed to adequately clear the infection or improve symptoms
- surgical valve repair (rarely done): surgical valvuloplasty (commissurotomy, annuloplasty), tissue patch
- surgical valve replacement: typically for aortic and mitral valves
- surgical decision between mechanical vs. bioprosthetic prosthesis for patients 50-70 y/o remains uncertain as valve techniques evolve

Choice of Valve Prosthesis

Table 17. Mechanical Valve vs. Bioprosthetic Valve vs. Pulmonary Autograft-Ross Procedure

Type of Valve	Mechanical Valve	Bioprosthetic Valve	Pulmonary Autograft in Aortic Position (Ross Procedure*)
Valve Durability	Good durability	Limited long-term durability (mitral<aortic)	Only aortic valve replacement that restores life expectancy to the age- and sex-matched general population
Aortic Root	Less preferred in small aortic root sizes	Good flow in small aortic root sizes	Closest flow profile to native aortic roots
Risk of Thromboembolism	Increased risk of thromboembolism (1-3%/yr): requires long-term anticoagulation with coumadin	Decreased risk of thromboembolism: long-term anticoagulation not needed for aortic valves	Low risk of thromboembolism
Anticoagulation Requirements	Target INR - aortic valves: 2.0-3.0 (mean 2.5); mitral valves: 2.5-3.5 (mean 3.0)	Some recommendation for limited anticoagulation for mitral valves	No anticoagulation required, enables higher activity and straightforward pregnancies
Risk of Hemorrhage	Increased risk of hemorrhage: 1-2%/yr	Decreased risk of hemorrhage	Low risk of hemorrhage
Patient Age	<50 yr for aortic valves and <65 for mitral valves	>65 yr for both aortic and mitral valves	Classically in children and young adults <50 yr

*should only be performed in high volume centers with extensive experience in aortic root procedures and the Ross operation

Twenty-Year Outcome After Mitral Repair Versus Replacement for Severe Degenerative Mitral Regurgitation: Analysis of a Large, Prospective, Multicenter, International Registry
Circulation 2017;135:410-22
Purpose: Analyze very-long term outcomes after MV repair and replacement for degenerative MR with a flail leaflet.
Methods: Employing the Mitral Regurgitation International Database, outcomes after MV repair and replacement were analyzed by propensity score matching and by inverse probability-of-treatment weighting.
Results: Operative mortality was lower after MV repair than replacement in the propensity-matched population (0.2% vs. 4.4%; P<0.001) and 20-yr survival was better after MV repair than replacement in the same population (41% vs. 24%; P<0.001). MV repair was also associated with a reduced rate of valvular complications.
Conclusions: MV repair was associated with lower operative mortality, better 20-yr survival and lower complication rates than MV replacement, in patients with degenerative mitral regurgitation with a flail leaflet.

Prosthetic Valve Management

Management and Follow-Up

- follow-up: dependent on valve type, residual heart disease, and clinical factors
  - TTE after prosthetic valve implantation to assess hemodynamics and ventricular function
    - if/when clinical symptoms or signs of prosthetic valve dysfunction arise, repeat TTE; additional investigations may be warranted if high clinical suspicion is present
    - TTE at 5 yr, 10 yr, and then annually thereafter is reasonable in otherwise asymptomatic patients with a surgically implanted bioprosthetic valve (if transcatheter implantation was used, annual TTE following the procedure is reasonable)
  - optimal dental care and endocarditis prophylaxis are required
- antithrombotic therapy: risk of bleeding must be considered and balanced whenever using/increasing any antithrombotic therapy
  - for patients with a mechanical valve, use anticoagulation with a vitamin K antagonist and INR monitoring
  - for patients with a bioprosthetic TAVI, bioprosthetic SAVR, or mitral valve replacement, short term other antithrombotic oral anticoagulation or antiplatelet therapies may be indicated

Prosthetic Valve-Related Complications

- prosthetic valve dysfunction
  - no known medical therapies to prevent bioprosthetic or mechanical valve degeneration
  - etiology: tissue degeneration, pannus formation, IE, thrombosis
  - presentation: prosthetic vascular stenosis or regurgitation
  - investigations and treatment: depend on the type/severity of pathology, as well as patient characteristics (see below)
- thromboembolic events
  - ensure to assess anticoagulation adequacy, time spent in therapeutic range; rule out infective endocarditis; screen for new-onset AF; consider other sources of a potentially underlying hypercoagulable state
  - patients with a mechanical aortic/mitral valve that were in therapeutic INR range on a vitamin K antagonist at the time of event: consider increasing INR goal or adding low-dose daily aspirin
  - patients with a bioprosthetic aortic/mitral valve that were on antiplatelet therapy at time of event: consider switching to vitamin K antagonist anticoagulation
- valve thrombosis
  - mechanical valve thrombosis (generally a subacute-acute event):
    - often associated with inadequate anticoagulation; leads to rapid valve dysfunction
      - recurrent thrombosis can be associated with pannus ingrowth
    - symptoms/signs/presentation: rapid onset of symptoms, acute pulmonary edema, stenotic murmur, muffled closing clicks
    - investigations: urgent multimodal imaging (TTE, TEE, fluoroscopy and/or multidetector CT imaging)
    - treatment: if thrombosed valve is left-sided and symptoms of valve obstruction are present, treat urgently with either fibrinolytic therapy or emergency surgery
  - bioprosthetic valve thrombosis
    - most common in first 3 mo post-implantation; bioprosthetic valves are less thrombogenic than mechanical valves
    - investigations: TTE or TEE or 4D CT imaging in suspected patients
    - treatment: if suspected or confirmed, treatment with a vitamin K antagonist is reasonable (assuming hemodynamically stable and no contraindications)
- graft dysfunction after Ross operation
  - etiology: autograft dilatation and RVOT conduit stenosis and/or regurgitation
    - autograft within LVOT requires reintervention more often than pulmonary homograft within RVOT
  - presentation: aortic regurgitation, pulmonary stenosis, pulmonary regurgitation, aortic root aneurysm
  - investigations: echocardiography, MRI if aneurysmal root
  - treatment: when done in expert centers reintervention results in low mortality
    - autograft dilatation: reoperation (autograft is spareable in majority of cases and survival advantage is still preserved)
    - RVOT graft dysfunction: transcatheter pulmonary valve replacement or surgical pulmonary valve replacement (transcatheter is preferred)

Ross Operation

- En bloc removal of a patient's native pulmonary root with valve (autograft) and transposition of the autograft into the aortic position to a replace a diseased aortic valve that cannot be spared
- The RVOT is then reconstructed with a cadaveric pulmonary homograft
- With proper technique, mitigation of risk factors for early graft failure, and strict postoperative blood pressure control, the pulmonary autograft adapts to the hemodynamics of the LVOT and left heart with low rates of reintervention
- Despite being more complex than isolated aortic valve replacement, morbidity and mortality are comparable to AVR with bioprosthesis or mechanical valves when done in experienced centres

Mechanical or Biological Prostheses for Aortic-Valve and Mitral-Valve Replacement
NEJM 2017;377:1847-57
Purpose: To elucidate differences in mechanical vs. biological prostheses in aortic- and mitral-valve replacements.
Methods: Patients who underwent primary aortic-valve or mitral-valve replacement in California in the period from 1996-2013 were analyzed. Outcomes included long-term mortality and rates of re-operation, stroke, and bleeding.
Results: In aortic-valve replacement, biologic prosthesis was associated with higher 15-yr mortality than mechanical prosthesis among patients aged 45-54 yr (30.6% vs. 26.4%), but not among patients aged 55-64 yr. In mitral-valve replacement, biologic prosthesis was associated with higher mortality than mechanical prosthesis among patients aged 40-49 yr (44% vs. 21%), and among those aged 50-69 yr (50.0% vs. 45.3%).
Conclusion: The long term mortality benefit from mechanical versus biologic prosthesis persisted until 70 yr among mitral-valve replacement patients, and until 55 yr among aortic-valve replacement patients.

Ross Procedure Compared with Bioprosthetic Aortic Valve Replacement
J Am Coll Cardiol;2022;79(10):993–1005
Purpose: The study aimed to compare long-term outcomes in patients undergoing the Ross procedure versus those receiving bioprosthetic aortic valve replacements (AVR).
Methods: Consecutive patients aged 16-60 who underwent a Ross procedure (n=108) or surgical bioprosthetic AVR (n=108). Propensity score matching accounted for baseline differences. The primary outcome was all-cause mortality. The secondary outcomes included, valve reintervention, deterioration, endocarditis, thromboembolic events, and/or pacemaker implantation.
Results: The Ross procedure demonstrated a lower all-cause mortality (HR: 0. 35; 95% CI: 0.14-0.90; P = 0.028) compared to bioprosthetic AVR. When considering death as a competing risk, the Ross procedure was associated with decreased rates of reintervention (HR: 0.21; 95% CI: 0.10-0.41; P <0.001), valve deterioration (HR: 0.25; 95% CI: 0.14-0.45; P <0.001), thromboembolic events (HR: 0.15; 95% CI: 0.05-0.50; P = 0.002), and permanent pacemaker implantation (HR: 0.22; 95% CI: 0.07-0.64; P = 0.006).
Conclusion: In comparison to bioprosthetic AVR, the Ross procedure exhibited better superior long-term survival and a lower occurrence of adverse valve-related events.

Summary of Valvular Disease

General Principles for Evaluating Valvular Heart Disease

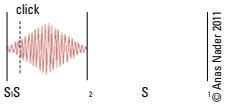
- initial evaluation
  - history and physical: symptom severity, valve disease, comorbidities, HF presence and severity
  - TTE (standard initial investigation): chamber size/function, valve morphology, severity of valvular heart disease, impacts to pulmonary/systemic circulations
  - ECG: rhythm, LVH, LV function
- further testing if indicated/needed
  - CXR: particularly useful for symptomatic patient; assesses for aortic and pericardial calcification, intrinsic pulmonary disease, heart size and congestion of the pulmonary vessels
  - TEE: assessment of mitral and prosthetic valve
  - CMR: LV volume/function, aortic disease, severity of valvular disease
  - PET CT: identification of infection/inflammation
  - stress testing: exercise capacity
  - catheterization: exercise- and drug-related hemodynamic responses, severity of valvular disease, pressures within the heart and pulmonary circulation
- future risk stratification
  - biomarkers: surrogate measure for myocardial damage and filling pressures
  - TTE strain: myocardial function
  - CMR: fibrosis
  - stress testing
  - procedural risk: The Society of Thoracic Surgeons (STS) and TAVI scores
  - frailty score
- preprocedural testing
  - dental exam: rule out sources of infection
  - invasive coronary angiogram or CT coronary angiogram
  - CT peripheral and cardiac (for transcatheter procedures)

Stages of Valvular Heart Disease

- stage A: at-risk (asymptomatic)
- stage B: progressive (mild-moderate severity; asymptomatic)
- stage C: asymptomatic, severe
  - C1: compensated LV or RV
  - C2: decompensated LV or RV
- stage D: symptomatic severe

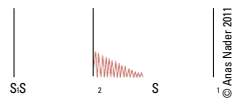
Table 18. Valvular Heart Disease

Aortic Stenosis



Etiology
Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease
Definition/Stages
Stage A: asymptomatic; congenital abnormality, bicuspid or sclerotic valve; aortic Vmax <2 m/s
Stage B: asymptomatic; can be mild AS (Vmax 2.0-2.9 m/s or mean pressure gradient <20 mm Hg) or moderate AS (Vmax 3.0-3.9 m/s or mean pressure gradient 20-39 mm Hg)
Stage C: asymptomatic; can be severe AS (Vmax ≥4 m/s or mean pressure gradient ≥40 mm Hg) or very severe AS (Vmax ≥5 m/s or mean pressure gradient ≥60 mm Hg) ± LV dysfunction
Stage D: symptomatic; can be severe AS or very severe AS; criteria also exist for low-flow, low-gradient AS with reduced LVEF and for low-gradient AS with either normal LVEF or paradoxical low-flow severe AS
Pathophysiology
Outflow obstruction ➔ increased EDP ➔ concentric LVH ➔ LV failure ➔ CHF, subendocardial ischemia
Symptoms
Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema, exertional dyspnea, decreased exercise tolerance, HF symptoms, presyncope, syncope
Physical Exam
Narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI
Auscultation: crescendo-decrescendo SEM radiating to right clavicle and carotid, musical quality at apex (Gallavardin phenomenon), S4, soft S2 with paradoxical splitting, S3 (late)
Investigations
ECG: LVH and strain, LBBB, LAE, AFib
CXR: post-stenotic aortic root dilatation, calcified valve, LVH, LAE, CHF
echo: etiology, valve area, valve morphology, hemodynamics, LV size, systolic function, prognosis, timing of intervention
Other: low-dose dobutamine stress testing, CT imaging/aortic valve calcium score, and exercise testing (contraindicated if symptomatic)
Treatment
Calcific AS: statin based on standard risk score for atherosclerotic prevention
Stages A-C: treat HTN
Asymptomatic: serial echos (repeated based on severity), avoid exertion
Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS
Procedural intervention considered in stage D, stage C, and other specific situations
Procedural Options
SAVR: if <65 yr old and >20 yr life expectancy, or if TAVR contraindication
- Conduct prior to pregnancy (if AS significant)
TAVR: if >80 yr old, if <10 yr life expectancy, or if high/prohibitive surgical risk
If patient between 65-80 yr old, decision between SAVR or TAVR is catered to specific patient
Percutaneous aortic balloon dilation: bridge to AVR in critical patients

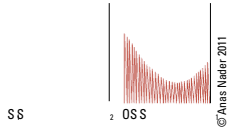
Aortic Regurgitation



Definition
Leakage of blood across the aortic valve into the LV (i.e. aortic insufficiency). May be primary or secondary AR
Etiology
Supravalvular: aortic root disease (Marfan syndrome, atherosclerosis and dissecting aneurysm, connective tissue disease)
Valvular: congenital (bicuspid aortic valve, large VSD), IE
Acute Onset: IE, aortic dissection, trauma, failed prosthetic valve
Pathophysiology
Volume overload ➔ LV dilatation ➔ increased SV, high sBP and low dBP ➔ increased wall tension ➔ pressure overload ➔ LVH (low dBP ➔ decreased coronary perfusion)
Symptoms
Usually only becomes symptomatic late in disease when HF symptoms, SOBOE, dyspnea, orthopnea, PND, syncope, and/or angina develop as a result of LV failure
Physical Exam
Waterhammer pulse, bisferiens pulse, femoral-brachial sBP >20 mmHg (Hill's test: wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex
Auscultation: early decrescendo diastolic murmur at LLSB (cusp pathology) or RLSB (aortic root pathology); best heard sitting, leaning forward, on full expiration; soft S1, absent S2, present S3 (late)
Investigations
ECG: LVH, LAE
CXR: LVH, LAE, aortic root dilatation
echo/TTE: etiology/severity, quantify AR, leaflet or aortic root anomalies, LV size, systolic function, prognosis, timing of intervention
TEE, CMR, or cardiac catheterization if ≥ moderate AR, suboptimal/inconsistent TTE: systolic function, heart volumes, aortic size, AR severity
Cardiac catheterization lab (Cath lab): if >40 yr and surgical candidate – to assess for ischemic heart disease
Exercise testing: hypotension with exercise
Treatment
Asymptomatic: serial echos, afterload reduction (e.g. ACEI, nifedipine, hydralazine)
Symptomatic: avoid exertion, treat CHF
Surgery if: symptomatic severe AR; chronic, severe AR with LVEF ≤55%; severe AR and otherwise undergoing cardiac surgery; other specific situations
Surgical Options
Valve replacement
Valve repair
Bentall procedure: replacement of aortic root and valve

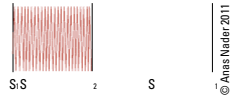
Table 18. Valvular Heart Disease

Mitral Stenosis



Etiology
rheumatic disease (most common), non-rheumatic calcification, congenital
Definition
Severe MS: mitral valve area (MVA) <1.5cm², diastolic pressure half-time ≥150 ms
Pathophysiology
MS → fixed CO and LAE → increased LA pressure → PVR and CHF; worse with AFib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)
Symptoms
SOBOE, orthopnea, fatigue, decreased exercise tolerance, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)
Physical Exam
AFib, left parasternal lift, palpable diastolic thrill at apex; if AFib, no "a" wave on JVP; if sinus, prominent "a" wave may be found on JVP
Auscultation: mid-diastolic rumble at apex; best heard with bell in left lateral decubitus position following exertion; loud S1, OS following loud P2 (heard best during expiration), long diastolic murmur, and short A2-OS interval correlate with worse MS
Investigations
ECG: NSR/AFib, LAE (P mitrale), RVH, RAD
CXR: LAE, CHF, mitral valve calcification
echo/TTE: diagnosis/severity, hemodynamics, valvular lesions, valve anatomy/morphology, LA thrombus if percutaneous mitral balloon commissurotomy being considered
Exercise testing: rheumatic MS and resting echo inconsistent with symptoms
Cath lab: if concurrent CAD and patient >40 yr (male) or >50 yr (female)
Treatment
Avoid exertion, fever (increased LA pressure); treat AFib and CHF; increase diastolic filling time (β-blockers, digitalis)
Vitamin K antagonist anticoagulation: in rheumatic MS if AF, previous embolism, or LA thrombus
Heart rate control (for some patients)
Intervention if: symptomatic, severe MS
Invasive Options
Percutaneous mitral balloon commissurotomy (PMBC): symptomatic, severe rheumatic MS with acceptable morphology, < moderate MR, and no LA thrombus (may be reasonable in other specific situations)
Mitral valve surgery (repair, commissurotomy, or replacement): symptomatic, severe rheumatic MS with contraindication/limited access for PMBC, previous failure of PMBC, or otherwise undergoing cardiac surgery (note: restenosis in 50% of patients in 8 yr after open mitral commissurotomy)
Nonrheumatic, calcific MS: if severe MS and severe symptoms, valve intervention can be contemplated pending discussion with patient about high procedural risk

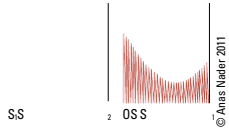
Mitral Regurgitation



Etiology
MVP, congenital cleft leaflets, LV dilatation/aneurysm (CHF, DCM, myocarditis), IE abscess, Marfan's syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease, leaflet perforation
Definition
Leakage of blood across the mitral valve from the LV into the LA; can be primary or secondary. Can use Carpentier's classification
Pathophysiology
Reduced CO → increased LV and LA pressure → LV and LA dilatation → and pulmonary HTN
Symptoms
Dyspnea, PND, orthopnea, palpitations, peripheral edema, decreased exercise tolerance, SOBOE
Physical Exam
Displaced hyperdynamic apex, left parasternal lift, apical thrill
Auscultation: holosystolic murmur at apex radiating to axilla ± mid-diastolic rumble, loud S2 (if pulmonary HTN), S3
Acute MR: sudden acute and hemodynamic instability (possibility during/post MI)
Investigations
ECG: LAE, left atrial delay (bifid P waves), ± LVH
CXR: LVH, LAE, pulmonary venous HTN
echo/TTE: etiology and severity of MR, LV/RV function, leaflets, pulmonary artery pressure, vegetations/abscesses, papillary muscle/chordal rupture, LA size, mitral valve apparatus, extent of remodelling
TEE: can be helpful with acute MR or if considering transcatheter interventions; also used when TTE findings are insufficient/inconsistent; assess for MR severity/mechanism and LV function
Swan-Ganz Catheter: prominent LA "v" wave
Other: CMR, exercise testing, stress nuclear/PET, stress echo. and serum biomarkers/novel measurement of LV function
Treatment
Acute MR: vasodilator therapy (use limited by systemic hypotension); intra-aortic balloon counter pulsation or percutaneous circulatory assist device may be employed
Asymptomatic: serial echos
Guideline-directed management and therapy for patients with severe MR and LV systolic dysfunction or HFrEF (e.g. ACEi, ARBs, beta blockers, aldosterone antagonists, ARNIs, biventricular pacing)
Intervention if: acute MR with CHF, papillary muscle rupture; severe MR with symptoms or LV systolic dysfunction; AFib; increasing LV size/presence of LV dilatation; pulmonary hypertension; decreasing exercise tolerance; can be reasonable in other situations if low mortality risk (<1%) and high probability of successful/durable repair (>95%) or if otherwise undergoing CABG
Procedural Options
Mitral valve surgery (preferably repair) is indicated and lifesaving in acute, severe, symptomatic, primary MR
Valve repair (preferred over replacement if degenerative disease is the etiology): >75% of patients with MR and myxomatous MVP – annuloplasty rings, leaflet repair, chordae transfers/shortening/replacement
Valve replacement if: failure of repair, heavily calcified annulus
Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation
Transcatheter edge-to-edge repair (TEER): reasonable in patients with severe, symptomatic primary MR with high/prohibitive surgical risk or in severe, symptomatic secondary MR if associated with LV dysfunction

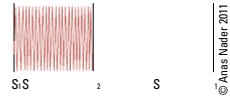
Table 18. Valvular Heart Disease

Tricuspid Stenosis



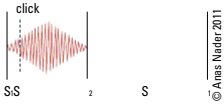
Etiology
Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS (in rheumatic heart disease), autoimmune disorders, atrial myxomas, blunt trauma, metastases, congenital, drug-associated valvulopathy
Definition
Tricuspid orifice narrowing; blood flow from the RA into the RV is obstructed
Pathophysiology
Increased RA pressure → right HF → CO decreased and fixed on exertion
Symptoms
Peripheral edema, fatigue, palpitations
Physical Exam
Prominent "a" waves in JVP, positive abdominojugular reflux, Kussmaul's sign, diastolic rumble 4th left intercostal space
Investigations
ECG: RAE
CXR: dilatation of RA without pulmonary artery enlargement
echo: diagnostic
Cardiac catheterization: large RA "a" wave (12-20 mm Hg); diastolic, mean pressure gradient of 4-8 mm Hg (Increased RA pressure with a slow decrease in early diastole + diastolic pressure gradient is classic for TS)
CMR: RV size/function
Treatment
Preload reduction (diuretics) for severe, symptomatic TS (caution: may exacerbate low output)
Treat underlying etiology
Slow HR
Surgery: usually performed at time of other cardiac surgery (e.g. mitral valve surgery for rheumatic MS)
Surgical Options
Valvotomy using 1-3 balloons
Valve surgery: repair or replacement (open or transcatheter options for replacement)
Usually tricuspid surgery favoured over percutaneous balloon tricuspid commissurotomy or valvuloplasty

Tricuspid Regurgitation



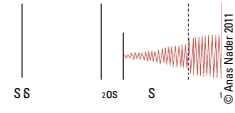
Etiology
RV dilatation, IE (particularly due to IV drug use), rheumatic disease, iatrogenic (device leads, endomyocardial biopsy), congenital (Ebstein's anomaly), pulmonary HTN, RV overload, DCM, annular dilation, leaflet tethering, RA dilatation, ischemic heart diseases, other (trauma, carcinoid, drugs, irradiation)
Definition
Leakage of blood across the tricuspid valve (i.e. tricuspid insufficiency); can be primary or secondary
Pathophysiology
RV dilatation → TR (and further RV dilatation)→ right HF
Symptoms
Peripheral edema, fatigue, palpitations, SOBOE, ascites
Physical Exam
elevated JVP, "cv" waves in JVP, positive abdominojugular reflux, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift,
Investigations
ECG: RAE, RVH, AFib
CXR: RAE, RV enlargement
echo/TTE: diagnostic – assess for etiology/severity of TR, IVC and right heart size, RV systolic function, left-sided disease and pulmonary artery systolic pressure
Invasive measurements (to address inconsistencies): cardiac index, right-sided diastolic pressure, pulmonary artery pressures, pulmonary vascular resistance, ventriculography
Treatment
Preload reduction (diuretics): reasonable if right-sided HF related to severe TR
Therapies to treat HF etiology reasonable if right-sided HF related to severe secondary TR
Surgery if: severe TR (stages C and D) and undergoing cardiac surgery for a left-sided valve; can be reasonable in other specific situations.
Surgical Options
Annuloplasty (i.e. repair; rarely replacement)

Pulmonary Stenosis



Etiology
Usually congenital, rheumatic disease (rare), carcinoid syndrome
Definition
Stiffening/narrowing of the pulmonic valve; blood flow into the pulmonary artery from the RV is obstructed
Pathophysiology
Increased RV pressure → RVH → right HF
Symptoms
Chest pain, syncope, fatigue, peripheral edema
Physical Exam
Systolic murmur at 2nd left intercostal space accentuated by inspiration; pulmonary ejection click; right-sided S4
Investigations
ECG: RVH
CXR: prominent pulmonary arteries, enlarged RV
echo: diagnostic
Treatment
Balloon valvuloplasty if severe symptoms
Surgical Options
Percutaneous or open balloon valvuloplasty

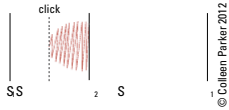
Pulmonary Regurgitation



Etiology
Pulmonary HTN, IE, rheumatic disease, tetralogy of Fallot (post-repair), defective valvular coaptation, annular dilatation, fibrinoid deposits
Definition
Insufficient closure of the pulmonic valve during diastole; reversal of flow into the RV
Pathophysiology
Increased RV volume → increased wall tension → RVH → right HF
Symptoms
Chest pain, syncope, fatigue, peripheral edema
Physical Exam
Early diastolic murmur at LLSB; Graham Steell (diastolic) murmur at 2nd and 3rd left intercostal space (increasing with inspiration)
Investigations
ECG: RVH
CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV
echo: diagnostic
Treatment
Rarely requires treatment; valve replacement (rarely done)
Surgical Options
Pulmonary valve replacement

Table 18. Valvular Heart Disease

Mitral Valve Prolapse



Etiology
Myxomatous degeneration of chordae; thick, bulky leaflets that crowd orifice; associated with connective tissue disorders; pectus excavatum; straight back syndrome, other MSK abnormalities; <3% of population
Definition
Valve leaflet(s) prolapse into the LA; common cause of MR. (i.e. click-murmur syndrome, Barlow's syndrome, billowing mitral valve leaflets, or floppy valve syndrome)
Pathophysiology
Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms. Generally benign; however, presentation may be with sudden cardiac death, infective endocarditis, or cerebrovascular accident
Symptoms
Can be asymptomatic. May have prolonged, stabbing chest pain or atypical chest discomfort; dyspnea; anxiety/panic attacks; palpitations; fatigue; presyncope, SOBOE, exercise intolerance; low blood pressure; syncope; orthostasis; mood changes; syncope
Physical Exam
Auscultation: mid-systolic click (diagnostic - due to billowing of mitral leaflet into LA and tensing of redundant valve tissue); followed by a mid to late systolic murmur at apex (murmur accentuated by Valsalva and diminished when patient squatting)
Investigations
ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy
echo: diagnostic – systolic displacement of mitral valve leaflets above mitral annulus into LA; assess mitral valve leaflet thickness
Cardiac catheterization/left ventriculography: if inconsistent clinical and echo findings; sometimes picks up MVP incidentally
Treatment
Asymptomatic: often no treatment; reassurance. If MR associated, follow-up annually; if not, follow-up q3-5 yr
Sinus rhythm and high-risk MVP: aspirin may be considered
Systemic embolism, recurrent TIAs despite aspirin, ischemic stroke, or AFib: anticoagulation
Symptomatic: β-blockers and avoidance of stimulants (e.g. caffeine) of significant palpitations; anticoagulation if AFib
Surgical Options
Mitral valve surgery (repair favoured over placement): if symptomatic and significant MR; may be reasonable if asymptomatic with MR and systolic HF
Transcatheter mitral valve repair considered if high/prohibitive surgical risk

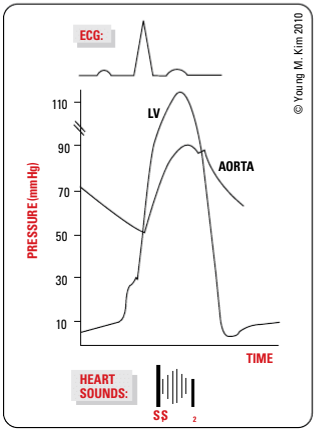


Figure 49. Hemodynamics of aortic stenosis
Stenosis across the aortic valve results in the generation of a significant pressure gradient between the LV and the aorta, as well as a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure, hence diminishing S2

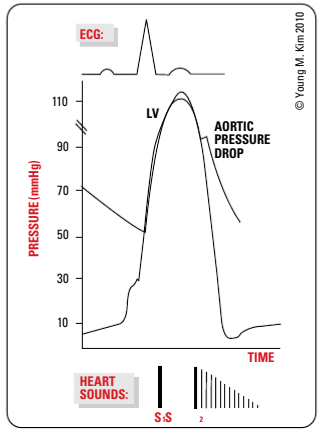


Figure 50. Hemodynamics of aortic regurgitation
Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2). The presence of regurgitant blood from the aorta increases LV end diastolic volume

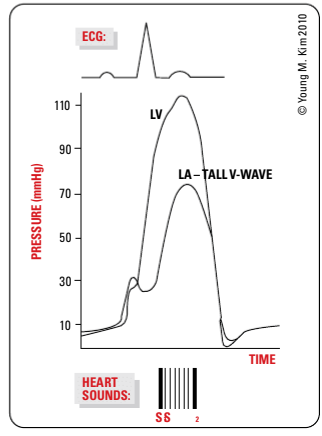


Figure 51. Hemodynamics of acute mitral regurgitation
During systolic contraction, blood regurgitates from the LV into the LA across the incompetent mitral valve resulting in a short but audible holosystolic murmur between S1 and S2. The portion of left ventricular end diastolic volume that regurgitates into the LA myocardium increases left atrial pressures resulting in a tall V-wave (in the JVP). Severe, acute MR usually results in acute hemodynamic decompensation

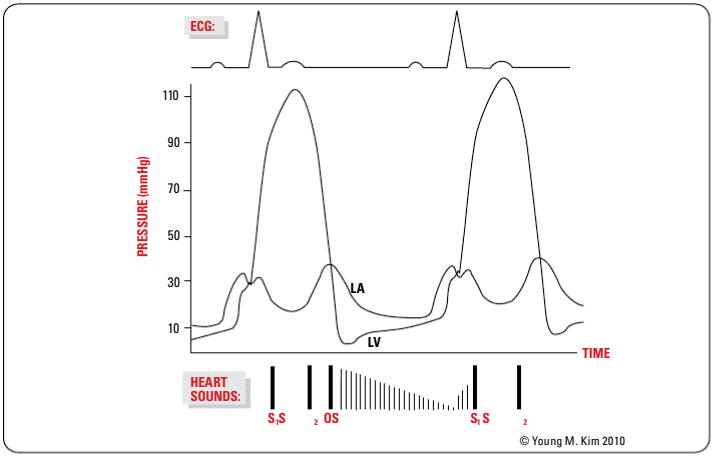


Figure 52. Hemodynamics of mitral stenosis
First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to MS and there is a consequent generation of a pressure gradient across the LA and LV. In diastole, the stenotic mitral valve opens (which corresponds to the OS) and the passage of blood across the MS results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible

Pericardial Disease

Acute Pericarditis

Definition

- syndrome involving the inflammation of the pericardium that may present with or without a pericardial effusion
- pericarditis can be divided into:
  - acute (<4-6 wk)
  - incessant (>4-6 wk with no remission)
  - recurrent (symptom-free remission period of 4-6 wk followed by new onset of pericarditis-associated signs and symptoms)
  - chronic (>3 mo)

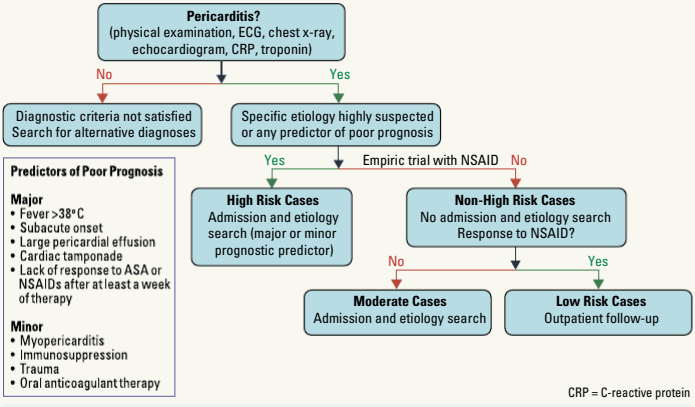
Etiology of Pericarditis/Pericardial Effusion

- idiopathic is most common (presumed to be viral)
  - searching for and identifying the etiology is not required in all patients; in nations with low TB prevalence, the most common causes of pericarditis are generally benign
    - infectious only approximately 14%
  - viral: Coxsackie virus A, B (most common), echovirus, Parvovirus B19, Epstein-Barr virus, HIV
  - bacterial: *S. pneumoniae, S. aureus, B. burgdorferi, M. tuberculosis*
- fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other cardiac procedures (e.g pacemaker insertion or TAVR), or other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma, lymphoma
- collagen vascular disease: SLE, polyarteritis, rheumatoid arthritis, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (e.g. sarcoidosis), vaccination (e.g. smallpox)
- autoimmune diseases
- immune checkpoint-inhibitor-associated pericarditis (severe; requires immunosuppressive therapy)
- see *Figure 53, C62* for a proposed approach to triaging pericarditis

Transcatheter (TAVR) or Surgical (SAVR) Aortic-Valve Replacement in Intermediate-Risk Patients (PARTNER II Trial)
NEJM 2016;374:1609-1620
Purpose: To determine if TAVR and SAVR result in different survival rates among intermediate-risk patients with AS.
Methods: Patients with AS were randomized to either TAVR (N=1011) or to SAVR (n=1021). The primary endpoint was death from any cause or disabling stroke at 2 yr.
Results: The death rate from any cause or disabling stroke was similar in the TAVR and SAVR groups (P=0.001 for noninferiority). In the transfemoral-access cohort, TAVR resulted in a lower rate of death or disabling stroke than SAVR did (P=0.05). In the transthoracic-access cohort, similar outcomes were observed in the TAVR and SAVR groups. TAVR resulted in larger aortic valve areas and lower rates of AKI, severe bleeding, and new onset AFib. Fewer major vascular complications and less paravalvular AR were observed in patients who underwent SAVR.
Conclusion: In intermediate-risk patients with AS, TAVR and SAVR resulted in similar rates of all-cause mortality and disabling stroke.

See Landmark Cardiology and Cardiac Surgery Trials table for more information on PARTNER III which details the outcomes of low-risk patients who underwent TAVR or surgical aortic-valve replacement.

Anterior Leaflet Laceration to Prevent Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement (LAMPOON)
J Am Coll Cardiol. 2019 Jul 30;74(4):595
Background: Transcathether mitral valve replacement (TMVR) is routinely employed in patients with valvular disease who are unsuitable for open surgical interventions. The primary complication of this procedure is LVOT obstruction as a result of the anterior mitral leaflet impinging on the interventricular septum.
Purpose: To study intentional laceration of the anterior mitral valve leaflet (LAMPOON) alongside TMVR to prevent the complication of LVOT obstruction.
Methods: Between June 2017 and June 2018, 30 patients with severe MR/MS, high surgical risk, and prohibitive risk of LVOT obstruction, underwent TMVR with LAMPOON. The primary outcomes were technical success for TMVR and LAMPOON (successful laceration) procedures, LVOT gradient <30 mmHg, freedom from emergent re-intervention, and procedural mortality.
Results: The LAMPOON laceration was deemed successful in 100% of enrolled patients. 100% of patients survived immediately post-procedure, with 93% surviving 30-d after discharge. 90% of patients had an LVOT gradient <30 mmHg (optimal range) after TMVR, with 100% of patients showing LVOT gradient <50 mmHg (acceptable range). The procedural success rate was 73% from the remaining 22 subjects.
Conclusions: In the studied population, LAMPOON mitigates the risk of LVOT obstruction with TMVR. LAMPOON is technically feasible and serves to enable TMVR in patients otherwise deemed ineligible due to prohibitive risk of LVOT obstruction.



Proposed triage of acute pericaditis accordint to epidemiological background and predictors of poor prognosis at presentation. At least one predictor of poor prognosis is sufficient to identify a high risk case. Major criteria have been validated by multivariate analysis, minor criteria are based on expert opinion and literature review. Cases with moderate risk are defined as cases without negative prognostic predictors but incomplete or lacking response to non-steroidal anti-inflammatory drug (NSAID) therapy. Low risk cases include those without negative prognostic predictors and good response to anti-inflammatory therapy. Specific etiology is intended as non-ideopathic etiology

Figure 53. Proposed triage of pericarditis

Transcatheter Mitral-Valve Repair in Patients with Heart Failure
NEJM. 2018;379:2307-18
Background: Patients with symptomatic HF and secondary mitral regurgitation have a poor prognosis. Repairing the mitral valve with tanscatheter mitral valve repair (TMVR) may improve patient outcomes.
Purpose: The study Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) assesses if TMVR improves clinical outcomes for patients with HF and MR due to LV dysfunction.
Methods: 614 patients with symptomatic HF and secondary mitral regurgitation with maximal medical therapy were randomized to TMVR with medical therapy, or medical therapy alone. The primary endpoint was hospitalization for HF within 24 mo.
Results: The primary endpoint was 35.8% per patient-year in the intervention group and 67.9% per patient-year in the control group (hazard ratio 0.53; 95% CI 0.40 to 0.70; P<0.001). Death from any cause occurred at 29.1% in the intervention group and 46.1% in the control group (hazard ratio 0.62; 95% CI 0.46 to 0.82; P<0.001).
Conclusions: TMVR in patients with symptomatic HF and secondary MR despite maximal medical therapy had a lower rate of hospitalization for HF as well as all cause mortality compared to medical therapy alone.

Clinical Presentation, Investigations, and Diagnosis

- 2 of the following 4 needed for diagnosis
  1. chest pain
     - sharp, rapid onset (may be dull or throbbing)
     - pain commonly radiates to the trapezius ridge
     - pleuritic; pain related to inspiration, coughing, and potentially hiccoughs
     - improves with sitting up/leaning forward
  2. pericardial friction rub
     - with patient leaning forward or on elbows and knees, friction rub heard on left sternal border
     - classically triphasic; may be mono- or biphasic
     - varies in intensity over time; repeated examinations necessary
     - highly specific finding
  3. ECG changes (only about 60% of patients have sequential changes)
     - stage 1: PR depression and generalized ST elevation (a generally specific finding but up to 40% have nondiagnostic and atypical changes)
     - stage 2: stage 1 findings reversed; J points on baseline prior to flattening of T waves
     - stage 3: inversion of T-waves
     - stage 4: all changes normalized
     - changes noted on ECG can be localized or diffuse; PR depression may be the only sign
  4. pericardial effusion (new or worsening)
- other physical exam findings: ± malaise, ± sinus tachycardia, ± low-grade fever, ± non-cardiac findings if the acute pericarditis is related with a systemic condition (e.g. rash, arthritis, weight loss, night sweats)
- other investigations may aid in diagnosis/monitoring
  - biomarkers/inflammatory markers
    - cardiac-specific troponin I or T elevation (≥30% of patients) –evidence of myocardial involvement (could be myopericarditis or perimyocarditis). Imaging modalities such as echo or CMR may also provide evidence of myocardial involvement
    - elevated CRP, ESR, and/or WBC count found in majority of patients, but not sensitive or specific (elevated high-sensitivity CRP can predict recurrence risk)
  - imaging
    - CXR
      - usually normal heart size (effusion >300 mL needed to increase cardiothoracic index)
      - patients with a new/unexplained increase in heart size should be worked up for acute pericarditis (especially when lung fields are clear)
      - may demonstrate evidence of pleuropericardial involvement in the setting of pleuropulmonary disease
      - cause of pericarditis can sometimes be identified

- echo: often the only necessary modality for imaging (TEE > TTE) → normal in 40%
  - applications include:
    - identifying pericarditis-associated complications (e.g. cardiac tamponade, constrictive pericarditis) or components of myocarditis (e.g. ventricular dysfunction)
    - monitoring pericardial effusion and efficacy of therapy
    - providing real-time evaluation during pericardial drainage
- CMR, CT may also have applications in the setting of pericarditis; assess for inflammation of pericardium

• differential diagnosis includes: Takotsubo syndrome, MI, myocarditis

Prognosis

• based on etiology (e.g. overall good prognosis = idiopathic/viral pericarditis (although significant recurrence risk), pericarditis with myocardial involvement; purulent and neoplastic pericarditis have a reported mortality rate between 20-30%)
  - negative prognostic factors: subacute onset, fever ≥38°C, >20mm pericardial effusion on echo, tamponade, lack of response following 1 wk of anti-inflammatory treatment → hospitalize patients with these factors and those with an elevated tamponade and/or constriction risk
    - minor negative prognostic factors: oral anticoagulation, trauma, immunosuppression

Treatment

• treat the underlying disease
• anti-inflammatory agents remain the mainstay for treatment (e.g. NSAIDs/ASA)
  - ketorolac may be employed in patients with severe pain or patients unable to take oral medication; use should be limited to 5 d
• colchicine may reduce symptom persistence and recurrent rates
• corticosteroid use is controversial but may be indicated in patients with incomplete response, failure of other anti-inflammatory medications, and/or other indicated situations (e.g. autoimmune disease-associated or immune checkpoint inhibitor-associated pericarditis)
• purulent pericarditis (rare but life-threatening): pericardial drainage and antimicrobial therapy catered to the culprit etiologic agent and/or local fibrinolytic therapy
• tuberculous pericarditis: multidrug regimen for several months (corticosteroids and pericardiectomy sometimes considered)
• pericarditis in the setting of viremia (particularly in immunocompromised patients): antiviral treatment
  - physical activity restriction until symptom resolution

Complications

• recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

Pericardial Effusion

Definition

• fluid accumulation in the pericardial sac (note: the pericardial sac normally hosts 10-50 mL of lubricating pericardial fluid). The composition of the fluid can include exudate, transudate, blood, and rarely air/gas

Etiology and Classification

• effusion is found incidentally on x-ray or echo for a significant proportion of patients
  - for these patients in developed countries, etiologies include:
    - idiopathic (up to 50%)
    - cancer (10-25%)
    - infections (15-30%)
    - iatrogenic causes (15-20%)
    - connective tissue diseases (5-15%)
  - in developing countries, TB is the predominant cause (>60%)
• for pericardial effusion with pericarditis, the prevalence of malignant/infectious etiologies is 15-50%
• transudative causes
  - increased systemic venous pressure or hydrostatic pressure: CHF, pulmonary HTN
  - decreased plasma oncotic pressure: cirrhosis, nephrotic syndrome, hypoalbuminemia/ hypoproteinemia
• exudative causes (serosanguinous or bloody)
  - pathologic process → inflammation → possible increased production of pericardial fluid
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
• can be classified according to onset, distribution, hemodynamic impact, composition, and size
• physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

Signs and Symptoms

- rate of development of pericardial effusion determines clinical presentation
- may be asymptomatic or similar to acute pericarditis
- classic symptoms: dyspnea on exertion (progressing to orthopnea), chest pain, and/or fullness
- symptoms related to local compression of extracardiac structures may include: nausea, dysphagia, hoarseness, hiccoughs; may cause esophageal/recurrent laryngeal nerve/trachea-bronchial/phrenic nerve irritation
- non-specific symptoms related to compression of related structures or reduced blood pressure and secondary sinus tachycardia: cough, weakness, fatigue, anorexia, palpitations, fever (may be associated with pericarditis)
- physical exam findings:
  - JVP increased with dominant "x" descent
  - arterial pulse normal-to-decreased volume; decreased pulse pressure
  - auscultation: distant heart sounds ± rub
  - Ewart's sign
  - often normal in patients without compromise to hemodynamic status; if tamponade present, findings can include fatigue, dyspnea, elevated JVP, neck vein distension, edema, pulsus paradoxus, muffled heart sounds (in moderate-large effusions). Rarely friction rubs heard (usually appreciated with concomitant pericarditis)

Ewart's Sign
Egophony, bronchial breathing, and dullness to percussion at the lower angle of the left scapula in pericardial effusion due to effusion compressing left lower lobe of lung

Investigations

- ECG: sinus tachycardia, low voltage (should raise concern for effusion with tamponade when present with sinus tachycardia; however, not specific for pericardial effusion), flat T waves, electrical alternans (highly specific for pericardial effusion (generally with tamponade), but not a sensitive enough sign to exclude effusion/tamponade)
  - be cautious in diagnosing STEMI in a patient with pericarditis and an effusion as antiplatelets may precipitate hemorrhagic effusion
- CXR: ± cardiomegaly with clear lung fields, ± rounded cardiac contour
- emergency room: bedside U/S with subxiphoid view showing fluid in pericardial sac
- echo/TTE (procedure of choice): fluid in pericardial sac; assess effusion size and hemodynamic effects, and assist in needle placement in pericardiocentesis
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, and investigating neoplastic involvement
- CT/CMR: compared with echo, provide greater field of view → enable loculated effusion detection, identification of masses or thickening associated with the pericardium, assessment for chest abnormalities (however, echo still preferred due to availability/portability/low cost)
- biomarkers: assessment of inflammation markers (e.g. CRP) recommended

Treatment (see *Figure 54, C65*)

- triage: based on size, hemodynamic effects (particularly assess for tamponade), inflammatory markers, concomitant pathologies → high risk patients should be admitted
- treat underlying etiology (60% of effusions associated with known disease)
- if inflammatory signs are present, or if associated with pericarditis, treat as if pericarditis; if elevated markers of inflammation, can try NSAIDs/colchicine/low-dose corticosteroids; if associated with systemic inflammation, Aspirin™/NSAIDs/colchicine recommended
- pericardiocentesis or cardiac surgery if: cardiac tamponade, symptomatic moderate-large effusion and unresponsive to medical therapy, or unknown bacterial/neoplastic etiology suspected
  - prolonged drainage using pericardiocentesis should also be considered if symptomatic effusion without evidence of inflammation or unresponsive to anti-inflammatory agents
  - if no inflammation and large, isolated effusion, pericardiocentesis alone may be required (no evidence for medical therapy), but recurrences are common
  - consider pericardiectomy or pericardial window (subxiphoid or video assisted thoracoscopic) if: re-accumulation of fluid, loculated effusion, biopsy required
- follow-up/frequent observation if no evidence/suspicion of:
  - tamponade
  - bacterial/neoplastic etiology
  - elevated inflammatory markers
  - associated pathology
  - large effusion (>20 mm)
    - Note: follow-up based on symptoms, effusion size and evolution, inflammatory markers, etc.

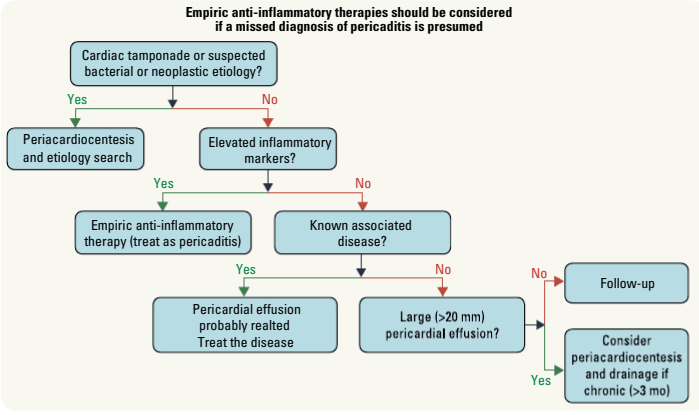


Figure 54. Triage/management algorithm for pericardial effusion

Cardiac Tamponade

Definition

- accumulation of fluid, pus, blood, clots or gas in the pericardium leading to life-threatening, slow or rapid compression of the heart

Classic Quartet of Tamponade
- Hypotension
- Increased JVP
- Tachycardia
- Pulsus paradoxus

Beck's Triad
- Hypotension
- Increased JVP
- Muffled heart sounds

Etiology

- can be caused by inflammation, trauma, rupture of the heart or aortic dissection
- major complication of rapidly accumulating pericardial effusion
- cardiac tamponade is a clinical diagnosis
- common causes: pericarditis, TB, iatrogenic, trauma, neoplasm/malignancy
- uncommon causes: collagen vascular diseases (e.g. SLE, rheumatoid arthritis, scleroderma), radiation, post-MI, uremia, aortic dissection, bacterial infection, pneumopericardium

Pathophysiology

- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

Signs and Symptoms

- tachycardia, hypotension, increased JVP
- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in sBP >10 mmHg during quiet breathing)
- JVP "x" descent only, blunted "y" descent
- hepatic congestion/peripheral edema
- severity of signs/symptoms depend on rate of accumulation, volume of pericardial contents, pericardial distensibility, cardiac filling pressures, and chamber compliance

Investigations

- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- CXR: enlarged cardiac silhouette; slow-accumulating effusions
- CT/CMR: less available; usually only necessary if Doppler echo is infeasible
- echo (diagnostic modality of choice): pericardial effusion (size, location, hemodynamic impact), swinging of the heart, compression of cardiac chambers (RA and RV) in diastole, etc. → echo also used for the purpose of guiding pericardiocentesis
- cardiac catheterization (rare)

Treatment

- urgent drainage: needle pericardiocentesis recommended (with echo or fluoroscopic guidance); surgery (i.e. pericardiotomy) is an alternative drainage approach (e.g. with purulent pericarditis or in an urgent situation involving bleeding into the pericardium)
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO) as well as mechanical ventilation
- IV fluid may increase CO
- treat underlying cause

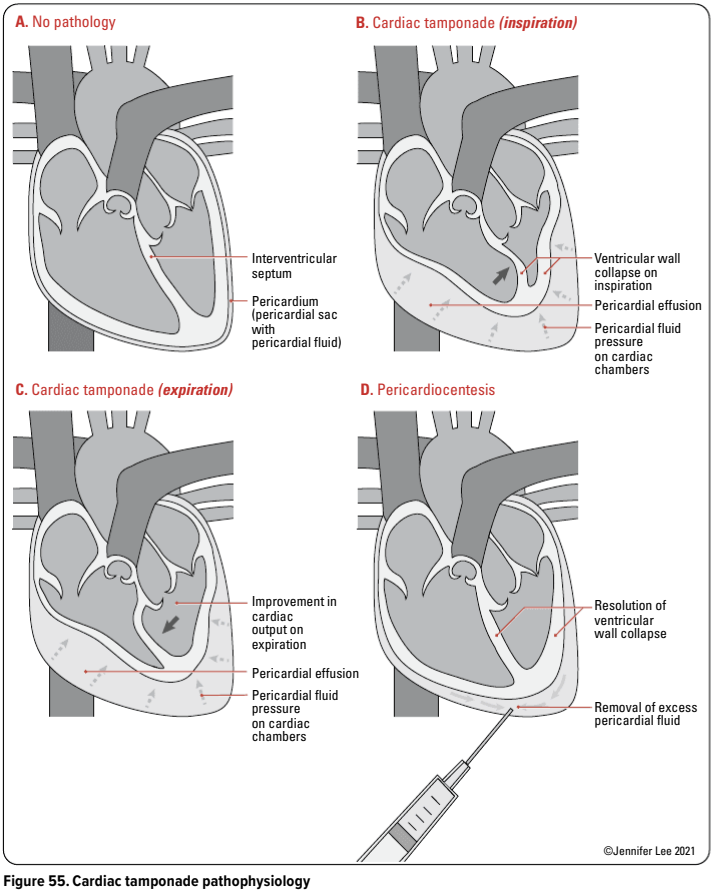

A. No pathology
Interventricular septum
Pericardium (pericardial sac with pericardial fluid)
B. Cardiac tamponade (inspiration)
Ventricular wall collapse on inspiration
Pericardial effusion
Pericardial fluid pressure on cardiac chambers
C. Cardiac tamponade (expiration)
Improvement in cardiac output on expiration
Pericardial effusion
Pericardial fluid pressure on cardiac chambers
D. Pericardiocentesis
Resolution of ventricular wall collapse
Removal of excess pericardial fluid
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Figure 55. Cardiac tamponade pathophysiology

Constrictive Pericarditis

Definition

- loss of pericardial elasticity caused by granulation tissue formation; leads to restricted ventricular filling

Etiology

- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, bacterial pericarditis/purulent pericarditis, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease
- any pericardial disease process can cause constrictive pericarditis; risk of progression to constrictive pericarditis is based on the etiology of the pericardial disease

Pathophysiology

- rigid, fibrous pericardium impairs ventricular filling during diastole → decreased venous return to the heart → rise in systemic venous pressure → signs and symptoms of right-sided HF (classically with preserved ventricular function and otherwise no myocardial disease)
  - in advanced cases, there can be systolic dysfunction if myocardial fibrosis or atrophy present

Signs and Symptoms
- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
  - venous congestion, ascites, hepatosplenomegaly, edema, pleural effusions
- increased JVP, Kussmaul's sign (paradoxical increase in JVP with inspiration), Friedreich's sign (prominent "y" descent)
- BP usually normal (and usually no pulsus paradoxus)
- precordial examination: ± pericardial knock (early diastolic sound)
- see *Table 19* for differentiation from cardiac tamponade

Investigations
- ECG: non-specific findings low voltage, flat T wave, ± AFib
- CXR: pericardial calcification, effusions
- echo/CT/CMR: pericardial thickening, calcification ± characteristic echo-Doppler findings (Note: CMR is discouraged if patient is hemodynamically impaired)
- cardiac catheterization: indicated if other, non-invasive imaging modalities are insufficient to make diagnosis; assess for equalization of end-diastolic chamber pressures
- diagnosis: right HF symptoms + diastolic filling impairment caused by constriction (documented on ≥1 imaging modality including echo, CT, CMR, and/or catheterization)
- note: in up to 20% of patients, constriction can occur even with normal thickness of the pericardium (pericardiectomy equally efficacious in these patients)

Treatment
- surgery (pericardiectomy): mainstay treatment for chronic, permanent constrictive pericarditis
- medical therapy: can be used in 3 situations
  1. for specific pathologies/etiologies (e.g. TB)
  2. for transient constriction that is temporarily caused by pericarditis, or new constriction diagnosis with evidence of inflammation of the pericardium (use anti-inflammatories)
  3. supportive when high/prohibitive surgical risk (goal is to relieve congestive symptoms with diuretics, salt restriction)
- prognosis best with idiopathic or infectious cause and worst in post-radiation
- death may result from HF

Table 19. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade

Characteristic	Constrictive Pericarditis	Cardiac Tamponade
JVP	"y" > "x"	"x" > "y"
Kussmaul's sign	Present	Absent
Pulsus paradoxus	Uncommon	Always
Pericardial knock	Present	Absent
Hypotension	Variable	Severe

DDx Pulsus Paradoxus
- Most etiologies of RV failure except restrictive cardiomyopathy (e.g. acute RV MI)
- Constrictive pericarditis (rarely)
- Severe obstructive pulmonary disease (e.g. asthma)
- Pneumothorax
- PE
- Cardiogenic shock
- Cardiac tamponade
- Effusive-Constrictive pericarditis

Extracorporeal Circulation

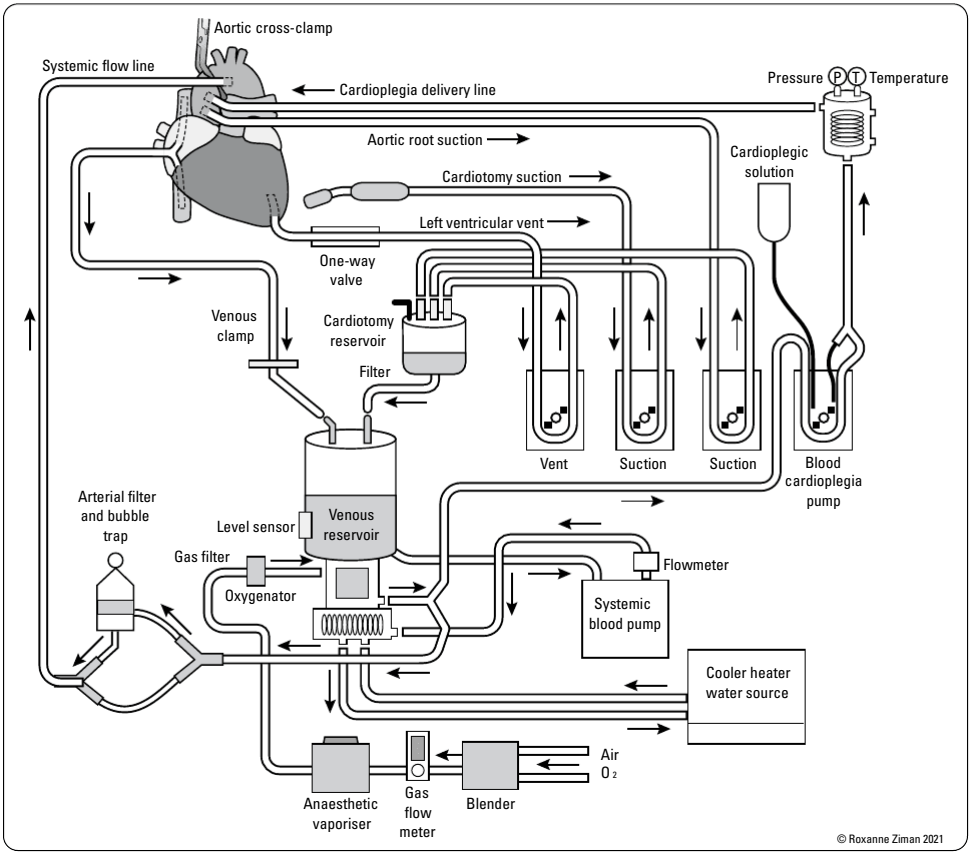

Figure 56. Cardiopulmonary bypass schematic
Modified from Cardiac Surgery in the Adult, second edition, Robert A.E Dion, p. 729, Copyright (2020), with permission from Elsevier

Cardiopulmonary Bypass

Overview
- CPB is commonly used in cardiac and thoracic aortic surgeries to obtain a still, bloodless surgical field by circumventing the heart and lungs while supplying blood to the systemic circulation
- essential functions of CPB: oxygenation, ventilation, circulation, temperature control

Components
- the standard components of a CPB circuit:
  - arterial cannula (aortic, femoral, or axillary) and line (3/8" heparin-coated tubing)
  - oxygenator (membrane oxygenator, defoamer, and heat exchanger)
  - pump (peristaltic/roller or centrifugal)
  - venous cannula (RA, SVC and IVC, or femoral) and line (1/2" heparin-coated tubing)
  - venous reservoir (rigid high capacitance reservoir or closed soft reservoir)

Mechanics
- venous blood is drained into venous reservoir. The blood is oxygenated, and CO_2 is eliminated, heated, or cooled (if applicable) and returned to the systemic circulation via the arterial cannula
  - heparin is first administered so that pump suckers can be turned on when the patient's ACT is >400 s and CPB initiated when ACT is >480 s
    - ACT is measured every 30 min while on CPB and additional heparin boluses are administered to maintain ACT >480 s
    - anticoagulation is reversed following separation of CPB by administering protamine which neutralizes heparin
  - the rate of blood draining into the venous reservoir is determined by the: CVP, height differential between venous cannula and venous reservoir, luminal radius of venous cannula and tubing, presence of air within the tubing
  - arterial cannulation is typically performed at the distal ascending aorta, distal to the aortic cross clamp, with alternative sites for cannulation including the aortic arch, innominate artery, subclavian artery, axillary artery, femoral artery, and LV apex
  - optimal flow rate is calculated to achieve a cardiac index of 2.4 L/min/m^2
  - patient parameters measured during CPB: ECG, BP, CVP, SaO_2, $ETCO_2$, peripheral and core temperature, urine output, ABG
  - CPB pump parameters measured during CPB: blood flow rate, roller pump/centrifugal speed, gas flow, pump blood temperature, heat exchanger water temperature, arterial line pressure, arterial and venous line O2 saturations, delivered O_2 concentration

Complications
- reaction to non-endothelialized foreign surfaces: systemic inflammatory response, hemolysis, coagulopathy
- vessel injury from cannulation: aortic dissection and embolization of aortic debris (e.g. porcelain aorta)
- heparin-related: heparin-associated thrombocytopenia, heparin-induced thrombocytopenia (HIT)
- systemic embolization: cerebrovascular accident, renal and splanchnic hypoperfusion
  - includes biologic and nonbiologic microemboli as well as air/gas/bubble emboli
  - cardiotomy reservoir must be filtered to reduce risk of microemboli

Cardiac and Neurological Protection during Cardiopulmonary Bypass

Myocardial Protection Techniques
- myocardial protection reduces myocardial ischemia during CPB by reducing myocardial oxygen consumption and maintaining oxygenated myocardial perfusion
- methods of myocardial protection to reduce oxygen demands include: unloading the heart (CPB), stopping the heart (cardioplegic diastolic arrest), cooling the heart (core hypothermia, cold saline external washing, hypothermic cardioplegia solutions)
- cardioplegia (given continuously or intermittently) induces diastolic arrest by altering myocytes' resting potential and ionic gradients via concentrated K+ solutions
  - crystalloid cardioplegia
    - extracellular solutions (high sodium) (e.g. St. Thomas' solution, del Nido solution) increase extracellular K+ concentration to prevent cardiomyocyte repolarization
    - intracellular solutions (low sodium) lower extracellular Na+ concentration thereby blocking depolarization
  - blood cardioplegia: autologous cold blood combined with tailored crystalloid solutions in various ratios
    - blood typically comprises majority of overall solution (e.g. 8:1, 4:1, 2:1)

Special Consideration of Blood Conservation for Jehovah's Witness Patients
- Preoperatively:
  - Administer erythropoietin
  - Stop all anticoagulant and antiplatelet medications for 7 d, if possible
- Intraoperatively:
  - Continuous cell salvage circuit
  - Meticulous hemostasis
  - OPCAB
  - Pharmacological adjuncts (tranexamic acid or aprotinin)
- Postoperatively:
  - Low threshold for resternotomy due to bleeding

Cerebral Protection

- cerebral protection techniques are required when CPB cannot supply the head vessels, such as during surgery on the aortic arch
- methods of cerebral protection to reduce oxygen demands include: hypothermia (most important) and anterograde/retrograde cerebral perfusion

Deep Hypothermic Circulatory Arrest

- deep hypothermic circulatory arrest reduces cerebral metabolism and oxygen consumption to the point that CPB can be discontinued
  - (30-40 min safe circulatory arrest at 20°C; 45-60 min safe circulatory arrest at 16°C)
    - concurrent ACP enables circulatory arrest at higher temperatures than DHCA alone
  - EEG monitoring occurs throughout to confirm adequate cerebral protection
  - mannitol (reduces cerebral edema) and steroids (decrease cerebral inflammation) are used adjunctively
  - complications related to deep hypothermic circulatory arrest include: coagulopathy and platelet dysfunction, systemic inflammatory response, neurological injury secondary to ischemia in watershed areas (neurologic dysfunction may be persistent or transient depending on etiology)

Common Medications

Table 20. Commonly Used Cardiac Therapeutics

Drug Class	Examples	Mechanism of Action	Indications	Contraindications	Side Effects
ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)					
	enalapril, perindopril, ramipril, lisinopril	Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis	HTN, CAD, CHF, post-MI, DM	Bilateral renal artery stenosis, pregnancy, caution in decreased GFR	Dry cough (10%), hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)					
	candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	Block AT II receptors, causing similar effects as ACEI	Same as ACEI, although evidence is generally less for ARBs; often used when ACEI are not tolerated	Same as ACEI	Similar to ACEI, but less likely to cause dry cough
ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)					
	sacubitril/valsartan	Sacubitril inhibits neprilysin which leads to vasodilation and natriuresis Valsartan (ARB) - see above	HFrEF	Angioedema, pregnancy	Angioedema, hyperkalemia, hypotension, renal insufficiency
β-BLOCKERS					
β1 antagonists β1/β2 antagonists α1/β1/β2 antagonists β1 antagonists with intrinsic sympathomimetic activity	atenolol, metoprolol, bisoprolol, propranolol, labetalol, carvedilol, acebutolol	Block β-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand; also slow conduction through the AV node	HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AFib, SVT	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension Caution in asthma, claudication, Raynaud's phenomenon, and decompensated CHF	Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud's phenomenon, and claudication
CALCIUM CHANNEL BLOCKERS					
Benzothiazepines Phenylalkylamines (non-dihydropyridines)	diltiazem, verapamil	Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers Also vasodilate	HTN, CAD, SVT, AFib, diastolic dysfunction	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, CHF	Hypotension, bradycardia, edema
Dihydropyridines	amlodipine, nifedipine, felodipine	Block smooth muscle calcium channels causing peripheral vasodilation	HTN, CAD	Severe AS and liver failure	Hypotension, edema, flushing, headache, light-headedness
SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS					
	canagliflozin dapagliflozin empagliflozin ertugliflozin	Proposed mechanisms include: osmotic diuresis and natriuresis reducing preload; vasodilation leading to reduced afterload; myocardial metabolic stabilization	Dapagliflozin trial (DAPA-HF) indicates potential use in HFrEF with DM/non-DM, with multiple other SGLT2 inhibitors trials underway. Although dapagliflozin has received guideline recommendations in Canada, US and EU for use in HFrEF, no SGLT2 inhibitors have formal approval for HFrEF without DM by Health Canada HFpEF (see EMPEROR-Preserved trial)	Severe CKD (dapagliflozin contraindicated in patients with eGFR <30 mL/min/1.73m2), T1DM, history of DKA, advise holding during sick days	Yeast infections, Urinary tract infections, hypoglycemic episodes, diabetic ketoacidosis, decreased bone mineral density

Table 20. Commonly Used Cardiac Therapeutics

Drug Class	Examples	Mechanism of Action	Indications	Contraindications	Side Effects
DIURETICS					
Thiazides	hydrochlorothiazide, chlorthalidone, metolazone	Reduce Na^+ reabsorption in the distal convoluted tubule (DCT)	HTN (drugs of choice for uncomplicated HTN)	Sulfa allergy, pregnancy	Hypotension, hypokalemia, polyuria
Loop diuretics	furosemide (Lasix®)	Blocks Na^+/K^+-ATPase in thick ascending limb of the loop of Henle	CHF, pulmonary or peripheral edema	Hypovolemia, hypokalemia	Hypovolemia, hypokalemic metabolic alkalosis
Mineralocorticoid receptor antagonists	spironolactone eplenerone	Antagonize aldosterone receptors	HTN, CHF, hypokalemia	Renal insufficiency, hyperkalemia, pregnancy	Edema, hyperkalemia, gynecomastia
INOTROPES					
	digoxin (Lanoxin®)	Inhibit Na^+/K^+-ATPase, leading to increased intracellular Na^+ and Ca $^{2+}$concentration, and increased myocardial contractility Also slows conduction through the AV node	CHF, AFib	2nd or 3rd degree AV block, hypokalemia	AV block, junctional tachycardia, bidirectional VT, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, N/V
ANTICOAGULANTS					
Coumarins	warfarin (Coumadin®)	Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X	AFib, LV dysfunction, prosthetic valves, venous thrombosis	Recent surgery or bleeding, bleeding diathesis, pregnancy	Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis
Heparins	Unfractionated heparin LMWHs: dalteparin, enoxaparin, tinzaparin	Antithrombin III agonist, leading to decreased clotting factor activity	Acute MI/ACS; (when immediate anticoagulant effect needed), PE, venous thrombosis	Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)	Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs)
Direct thrombin inhibitors	dabigatran	Competitive, direct thrombin inhibitor, thrombin enables fibrinogen conversion to fibrin during the coagulation cascade	AFib, venous thrombosis, PE	Severe renal impairment, recent surgery, active bleeding Idarucizumab: FDA approved agent for reversal of dabigatran for bleeding	Bleeding, GI upset
Direct factor Xa inhibitors	rivaroxaban apixaban edoxaban	Direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways	AFib, venous thrombosis, PE	Hepatic disease, active bleeding, bleeding diathesis, pregnancy, lactation Andexanet alfa FDA approved agent for reversal of apixaban and rivaroxaban for bleeding	Bleeding, elevated liver enzymes
ANTIPLATELETS					
Salicylates	ASA (Aspirin®)	Irreversibly acetylates platelet COX-1, preventing thromboxane A2-mediated platelet aggregation	CAD, acute MI, post-MI, post-PCI, CABG	Active bleeding or PUD	Bleeding, GI upset, GI ulceration, impaired renal perfusion
Thienopyridines	clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®)	P2Y12 antagonist (block platelet ADP receptors	Acute MI, post-MI, post-PCI, CABG	Active bleeding or PUD	Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)
Nucleoside analogues	ticagrelor (Brilinta®)	P2Y12 antagonist (but different binding site than thienopyridines)			
Glycoprotein IIb/IIIa inhibitors	eptifibatide, tirofiban, abciximab	Block binding of fibrinogen to Gp IIb/IIIa	Acute MI, particularly if PCI is planned	Recent surgery or bleeding, bleeding diathesis	Bleeding
THROMBOLYTICS					
	alteplase, reteplase, tenecteplase, streptokinase	Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin	Acute STEMI	See *Table 10, C34*	Bleeding
NITRATES					
	nitroglycerin	Relax vascular smooth muscle, producing venous and arteriolar dilation	CAD, MI, CHF (isosorbide dinitrate plus hydralazine)	Concurrent use of cyclic guanosine monophosphate phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure	Headache, dizziness, weakness, postural hypotension

Table 20. Commonly Used Cardiac Therapeutics

Drug Class	Examples	Mechanism of Action	Indications	Contraindications	Side Effects
LIPID LOWERING AGENTS					
Statins	atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Meracor®)	Inhibit hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase, an enzyme which catalyzes the rate-limiting step in cholesterol synthesis	Dyslipidemia (1° prevention of CAD), CAD, post-MI (2° prevention of CV events)	Liver or muscle disease	Myalgia, rhabdomyolysis, abdominal pain
Cholesterol absorption inhibitor	ezetimibe (Ezetrol®)	Inhibits gut absorption of cholesterol	Decreases low-density lipoprotein but does not reduce mortality	Liver or renal impairment	Myalgia, rhabdomyolysis, abdominal pain
PCSK9 inhibitor	evolocumab alirocumab	Monoclonal antibody that inhibits PCSK9's inhibitory action on the recycling of LDL receptors, thereby increasing the number of LDL receptors on the surface of liver cells	Hypercholesterolemia	Hypersensitivity reaction to drug	Mild reactions to site of injection, nasopharyngitis
Miscellaneous	fibrates, bile acid sequestrates, nicotinic acid		Primarily in familial hypercholesterolemia		GI side effects common

Antiarrhythmics

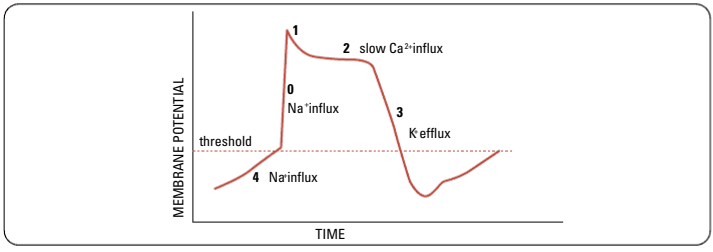

Figure 57. Representative cardiac action potential

Table 21. Antiarrhythmic* Drugs (Vaughan-Williams Classification)

Class	Agent	Indications	Side Effects	Mechanism of Action
Ia	quinidine procainamide disopyramide	SVT, VT	Torsades de Pointes (all Ia), diarrhea Lupus-like syndrome Anticholinergic effects	Moderate Na^+ channel blockade Slows phase 0 upstroke Prolongs repolarization, slowing conduction
Ib	lidocaine mexiletine	VT	Confusion, stupor, seizures GI upset, tremor	Mild Na^+ channel blockade Shortens phase 3 repolarization
Ic	propafenone flecainide encainide	SVT, VT AFib	Exacerbation of VT (all Ic) Negative inotropy (all Ic) Bradycardia and heart block (all Ic)	Upstroke
II	propranolol metoprolol, etc.	SVT, AFib	Bronchospasm, negative inotropy, bradycardia, AV block, impotence, fatigue	β-blocker Decreases phase 4 depolarization
III	amiodarone** sotalol	SVT, VT AFib SVT, VT	Amiodarone: photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR Amiodarone and sotalol: Torsades de Pointes, bradycardia, heart block, β-blocker side effects	Blocks K^+ channel Prolongs phase 3 repolarization, which prolongs refractory period
IV	verapamil diltiazem	SVT AFib	Bradycardia, AV block Hypotension	CCB Slows phase 4 spontaneous depolarization, slowing AV node conduction

*All antiarrhythmics have potential to be proarrhythmic
**Amiodarone has class I, II, III, and IV properties

Table 22. Actions of α and β Adrenergic Receptors

	α RECEPTORS		β RECEPTORS	
Target System	α1	α2	β1	β2
Cardiovascular	Constriction of vascular smooth muscle Constriction of skin, skeletal muscle, and splanchnic vessels Increase myocardial contractility Decrease HR	Same as α1 Peripherally act to modulate vessel tone Vasoconstrict and dilate; oppose α1 vasoconstrictor activity	Increased myocardial contractility Accelerate SA node conduction Accelerate ectopic pacemakers	Decreased vascular smooth muscle tone
Respiratory				Bronchodilation
Dermal	Pilomotor smooth muscle contraction Apocrine constriction			
Ocular	Radial muscle contraction		Ciliary muscle relaxation	
Gastrointestinal	Inhibition of myenteric plexus Anal sphincter contraction			
Genitourinary	Pregnant uterine contraction Penile and seminal vesicle ejaculation Urinary bladder contraction	Smooth muscle wall relaxation	Stimulation of renal renin release	Bladder wall relaxation Uterine relaxation
Metabolic	Stimulate liver gluconeogenesis and glycogenolysis at the liver	Same as α1 Fat cell lipolysis	Fat cell lipolysis Glycogenolysis	Gluconeogenesis Fat cell lipolysis

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)

Table 23. Commonly Used Drugs that Act on α and β Adrenergic Receptors

	α RECEPTORS			β RECEPTORS		
Mechanism of Action	α1	α1 and α2	α2	β1	β1 and β2	β2
Agonist	Phenylephrine Methoxamine	Epinephrine Norepinephrine	Clonidine Methyldopa	Norepinephrine Dobutamine	Isoproterenol Epinephrine	Albuterol Terbutaline
Antagonist	Prazosin Phenoxybenzamine	Phentolamine	Yohimbine Mirtazapine	Metoprolol Acebutolol Alprenolol Atenolol Esmolol	Propranolol Timolol Nadolol Pindolol Carvedilol	Butoxamine

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)

Landmark Cardiac Trials

Trial Name	Reference	Clinical Trial Details
ASCVD/ISCHEMIC HEART DISEASE (Primary Prevention)		
HOPE (ACEi)	NEJM 2000;342:145-153	**Title**: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients Purpose: To investigate the impact of ramipril, an angiotensin-converting-enzyme inhibitor, on high-risk patients without left ventricular dysfunction or heart failure and their susceptibility to cardiovascular events. **Method**s: In a five-year study, 9,297 high-risk patients without HF were randomly assigned to receive ramipril or placebo. The primary outcome measured MI, stroke, or cardiovascular death. Vitamin E effects were analyzed separately. **Results**: In the trial, 651 out of 4,646 patients (14.0%) receiving ramipril reached the primary endpoint, compared to 826 out of 4,630 patients (17.8%) on placebo. Ramipril treatment resulted in reductions in cardiovascular death (6.1% vs. 8.1%), MI (9.9% vs. 12.3%), stroke (3.4% vs. 4.9%), overall mortality (10.4% vs. 12.2%), revascularization procedures (16.3% vs. 18.8%), cardiac arrest (0.8% vs. 1.3%), heart failure (9.1% vs. 11.6%), and diabetes-related complications (6.4% vs. 7.6%). **Conclusions**: Ramipril effectively lowers mortality, MI, and stroke rates in high-risk patients without preexisting low ejection fraction or HF.
DAPT(Antiplatelet)	NEJM 2014;371:2155-66	**Title**: Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents Purpose: Study the effects of dual antiplatelet therapy beyond 1 yr, to prevent thrombotic complications after drug-eluting stents. **Method**s: After 12 mo treatment with clopidogrel or prasugrel, patients were randomized to continuing this therapy or receiving placebo. The primary endpoints were stent thrombosis and major adverse CV events from 12-30 mo. **Results**: Continued treatment reduced the rates of stent thrombosis (0.4% vs. 1.4%; 95% CI 0.17 to 0.48; P<0.001), and major CV and cerebrovascular events (4.3% vs. 5.9%; 95% CI 0.59 to 0.85; P<0.001). The rate of moderate-severe bleeding was increased in the continued treatment group (2.5% vs. 1.65%; P=0.001). **Conclusions**: Dual antiplatelet therapy beyond 1 yr confers additional benefit.
ARRIVE (ASA)	Lancet 2018;392:1036-46	**Title**: Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE): A Randomised, Double-blind, Placebo-controlled Trial Purpose: Assess efficacy and safety of ASA versus placebo in patients with moderate risk of a first CV event. **Method**s: Patients with moderate CV risk were randomized to receive ECASA or placebo tablets, once daily. The primary endpoint was a composite of time to CV death, MI, UA, stroke, or TIA. **Results**: The primary endpoint occurred in 4.29% of ASA-treated patients versus 4.48% of placebo-treated patients (hazard ratio 0.96; 95% CI 0.81 to 1.13; P=0.6). The overall incidence of adverse events was similar between groups (82.01% in ASA group versus 81.72% in placebo group). **Conclusions**: Among patients at moderate risk of CHD, the use of ASA was not beneficial. ASA was not associated with a reduction in adverse CV events.
European Coronary Surgery Study (CABG vs medical therapy)	NEJM 1988;319:332-37	**Title**: Twelve-Year Follow-up of Survival in the Randomized European Coronary Surgery Study Purpose: Evaluate survival rates in men with good LVEF after CABG or medical therapy. **Method**s: 767 men were randomized to early CABG or medical therapy. **Results**: At the projected 5-yr follow-up period, there was a significantly higher survival rate in the surgical group than in the medical treatment group (92.4% vs. 83.1%, P=0.0001). **Conclusions**: CABG resulted in higher survival than medical therapy at 5-yr follow-up but not at 12-yr follow-up.
ASCOT-LLA (Statin)	Lancet 2003;361:1149-58	**Title**: Prevention of Coronary and Stroke Events with Atorvastatin in Hypertensive Patients who have Average or Lower-than-Average Cholesterol Concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-lla): A Multicentre Randomised Controlled Trial Purpose: Assess benefits of cholesterol lowering in primary prevention of CHD in hypertensive patients. **Method**s: Hypertensive patients aged 40-79 were randomized to atorvastatin 10 mg or placebo. The primary endpoint was non-fatal MI and fatal CHD after 5-yr follow-up. **Results**: 100 primary events occurred in the atorvastatin group compared to 154 events in the placebo group at a median follow-up of 3.3 yr (hazard ratio 0.64; 95% CI 0.50 to 0.83; P=0.0005). Fatal and non-fatal stroke, total CV events and total coronary events were also lowered in the atorvastatin group. **Conclusions**: In hypertensive patients with risk factors for CHD and average cholesterol levels. atorvastatin reduced non-fatal MI, fatal CHD, fatal/non-fatal stroke, coronary events but not all-cause mortality.
JUPITER	NEJM 2008;359:2195-207	**Title**: Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein Purpose: Evaluate the effects of statin treatment on CV events in patients with elevated CRP without hyperlipidemia . **Method**s: 17802 apparently healthy patients with LDL levels <130 mg/dL and CRP levels >2.0 mg were randomized to rosuvastatin 20 mg daily or placebo. The primary endpoint was a composite of MI, stroke, revascularization, hospitalization for UA, or CV death. **Results**: The rates of the primary endpoint were 0.77 and 1.36 per 100 person-years in the statin and placebo groups respectively (hazard ratio 0.56; 95% CI 0.46 to 0.69; P<0.00001). The rosuvastatin group did not have a significant increase in myopathy or cancer, but a higher rate of diabetes. **Conclusions**: With low to normal LDL and elevated high CRP, treatment with rosuvastatin significantly reduced major CV events.
ASCVD/ISCHEMIC HEART DISEASE (Secondary Prevention)		
EUROPA (ACEi)	Lancet 2003;362:782-88	**Title**: Efficacy of Perindopril in Reduction of Cardiovascular Events Among Patients with Stable Coronary Artery Disease: Randomised, Double-blind, Placebo-controlled, Multicentre Trial (The EUROPA Study) Purpose: Assess whether ACEI reduced CV risk in a low-risk population with stable coronary disease. **Method**s: After a run-in of 4 wk, in which all patients received perindopril, 12218 patients were randomized to perindopril 8 mg OD or matching placebo. The primary endpoint was CV death, MI, or cardiac arrest **Results**: 8% of perindopril patients experienced a primary endpoint, compared with 10% of placebo patients. These benefits were consistent in all subgroups and secondary endpoints. **Conclusions**: With stable CAD and no CHF, perindopril reduced CV death, MI, and total mortality.
COMPASS (Anticoagulant ± ASA)	NEJM 2017; 377:1319-1330	**Title**: Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease Purpose: Assess the efficacy of rivaroxaban in combination with ASA compared to ASA alone for secondary cardiovascular prevention **Method**s: 27, 394 patients with stable atherosclerosis were randomly assigned to receive rivaroxaban with ASA or ASA alone in a double-blind trial. Primary outcomes were CV death, stroke or MI. **Results**: Primary outcomes occurred 4.1% in rivaroxaban and ASA-treated group compared to 5.4% with ASA alone (hazard ratio 0.76; 95% CI, 0.66 to 0.86; p<0.001). More major bleeding occurred in the rivaroxaban and ASA-treated group compared to ASA alone (3.1% vs 1.9% hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). **Conclusions**: Rivaroxaban with ASA had better cardiovascular outcomes than ASA alone but resulted in more major bleeding.
CURE (Anticoagulant and ASA)	NEJM 2001;345:494-502	**Title**: Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation Purpose: Evaluate efficacy and safety of clopidogrel with ASA in patients with ACS without ST-elevation. **Method**s: 12562 patients who presented within 24 h of symptom onset were randomized to clopidogrel or placebo in addition to ASA for 3-12 mo. The primary endpoint was a composite of CV mortality, non-fatal MI, or stroke. **Results**: The primary endpoint occurred in 9.3% of clopidogrel patients and 11.4% of patients in the placebo group (RR 0.80; 95% CI 0.72 to 0.90; P<0.001). There were significantly more patients with bleeding in the clopidogrel group than the placebo group (3.7% vs. 2.7%; RR 1.38; P=0.001). **Conclusions**: Clopidogrel plus ASA reduced death from CV causes, non-fatal MI, or stroke but increased bleeding complications.
OASIS-5 (Anticoagulant and LMWH)	NEJM 2006;354:1464-76	**Title**: Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes Purpose: Assess whether fondaparinux would reduce bleeding risk while retaining the anti-ischemic benefits of enoxaparin. **Method**s: 20078 patients were randomized to receive either fondaparinux 2.5 mg daily, or enoxaparin 1 mg/kg twice daily. The primary outcomes were death, MI, refractory ischemia at 9 d, or bleeding. **Results**: The primary outcome rates were similar between the two groups (hazard ratio 1.01; 95% CI 0.90 to 1.13). The rate of 9-d major bleeding was lower in the fondaparinux group than the enoxaparin group (2.2% vs. 4.1%; hazard ratio 0.52; P<0.001). **Conclusions**: Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 d, and MI at 30 and 180 d.

Trial Name	Reference	Clinical Trial Details
ISCHEMIA (Angiography and revascularization vs. medical therapy)	NEJM 2020; 382:1395-1407	**Title**: Initial Invasive or Conservative Strategy for Stable Coronary Disease Purpose: Compare outcomes from invasive intervention and medical therapy vs medical therapy alone in patients with stable coronary disease and moderate or severe ischemia. **Method**s: 5179 patients with moderate or severe ischemia were randomly assigned to invasive therapy (angiography and revascularization) with medical therapy or medical therapy, with angiography if medical therapy failed. Primary outcome was death from CV causes, MI or hospitalization due to unstable angina, HF or resuscitated cardiac arrest. Secondary outcome was death due to CV causes or MI. **Results**: The rate of primary endpoint at 6 mo was 5.3% for the invasive strategy and 3.4% for the conservative strategy (95% CI, 0.8-3.0) and at 5 years 16.4% and 18.2%, respectively (95% CI -4.7 to 1.0). There were 145 and 144 death, respectively (hazard ratio, 1.05; 95% CI, 0.83 to 1.32). **Conclusions**: There was no evidence that initial invasive therapy compared to conservative therapy reduced the risk of ischemic CV events or death in patients with stable coronary artery disease and moderate or severe ischemia.
CAPRIE (Antiplatelet vs ASA)	Lancet 1996;348:1329-39	**Title**: A Randomised, Blinded, Trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) Purpose: Assess the relative efficacy of clopidogrel and ASA in reducing risk of clinical thrombotic events. **Method**s: Patients with atherosclerotic vascular disease were randomized to clopidogrel 75 mg once daily or ASA 325 mg once daily. Primary endpoints were a composite of ischemic stroke, MI, or vascular death. **Results**: Patients treated with clopidogrel had a 5.32% annual risk of stroke, MI or death, compared with 5.83% of ASA patients (p=0.043). There were no major differences in terms of safety. **Conclusions**: In atherosclerotic vascular disease, clopidogrel reduced the rates of stroke, MI, or vascular death compared to ASA.
COLCOT (Antiinflammatory)	NEJM 2019;381:2497-505	**Title**: Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction Purpose: Assess the efficacy and safety of low-dose colchicine after MI. **Method**s: Patients were randomized to receive 0.5 mg colchicine once daily or placebo. The primary endpoint was a composite of CV death, resuscitated cardiac arrest, MI, stroke, or UA leading to revascularization. **Results**: The primary endpoint occurred in 5.5% of colchicine-treated patients and 7.1% in the placebo group (hazard ratio 0.77; 95% CI 0.61 to 0.96; P=0.02). The hazard ratios were 0.84 for CV death, 0.83 for resuscitated cardiac arrest, 0.91 for MI, 0.26 for stroke, and 0.50 for UA. **Conclusions**: In patients with recent MI, colchicine lowered the risk of subsequent CV events as compared to placebo.
PEGASUS-TIMI 54 (Antiplatelet)	NEJM 2015;372:1791-800	**Title**: Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction Purpose: Investigate the safety and efficacy of ticagrelor after an ACS. **Method**s: 21162 patients who had a prior MI were randomized to ticagrelor 90 mg BID, or placebo. The primary endpoints were a composite of CV death, MI, or stroke. The primary safety endpoint was thrombolysis in MI and major bleeding. **Results**: Kaplan-Meier event rates showed that ticagrelor reduced event rates at 3 yr, at 7.77% for the treatment group and 9.04% in the placebo group (hazard ratio 0.85; 95% CI 0.75 to 0.96; P=0.008). Rates of major bleeding were higher with ticagrelor than with placebo (P<0.001). **Conclusions**: Ticagrelor on top of ASA reduces CV events in patients with a history of MI.
PLATO (Antiplatelet)	NEJM 2009;361:1045-57	**Title**: Ticagrelor vs. Clopidogrel in Patients with Acute Coronary Syndromes Purpose: Evaluate the efficacy of ticagrelor vs. clopidogrel in patients with an ACS. **Method**s: 18624 patients admitted to hospital with ACS, with or without ST-elevation, were randomized to ticagrelor (180 mg loading, 90 mg twice daily after) or clopidogrel (300-600 mg loading; 75 mg daily after). The primary endpoint was a composite of vascular death, MI, or strok. **Results**: The primary endpoint occurred in 9.8% of patients receiving ticagrelor, compared with 11.7% of patients receiving clopidogrel (hazard ratio 0.84; 95% CI 0.77 to 0.92; P<0.001). The rate of death was also reduced with ticagrelor (4.5% vs. 5.9%; P<0.001). There were no significant differences in the rates of major bleeding. **Conclusions**: In ACS patients with either STEMI or NSTEMI, regardless of reperfusion strategy, ticagrelor reduced mortality, MI, and stroke without increased bleeding compared to clopidogrel.
PLATO (Antiplatelet)	NEJM 2007;357:2001-15	**Title**: Prasugrel vs. Clopidogrel in Patients with Acute Coronary Syndromes Purpose: Compare clopidogrel and prasugrel in preventing thrombotic complications of ACS and PCI. **Method**s: 13608 patients with ACS and scheduled PCI were randomized to prasugrel (60 mg loading, 10 mg maintenance) or clopidogrel (300 mg loading, 75 mg maintenance). The primary endpoint was CV death, non-fatal MI, or non-fatal stroke. The safety endpoint was major bleeding. **Results**: The primary endpoint occurred in 12.1% of clopidogrel patients and 9.9% of prasugrel patients (hazard ratio 0.81; 95% CI 0.73 to 0.90; P<0.001). Major bleeding was observed in 2.4% of prasugrel patients and 1.8% of clopidogrel patients (hazard ratio 1.32; 95% CI 1.03 to 1.68; P=0.03.) **Conclusions**: In ACS patients scheduled for PCI, prasugrel reduced ischemic events but increased major bleeding compared to clopidogrel.
BHAT (β-Blocker)	JAMA 1982;247:1707-14	**Title**: A Randomized Trial of Propranolol in Patients with Acute Myocardial Infarction Purpose: Study the effects on mortality of administering propranolol hydrochloride in patients who experienced at least one M. **Method**s: 3387 patients were randomized to either propranolol or placebo for 21 d post-infarction. The primary outcome was all-cause mortality. **Results**: Total mortality during the average 25-mo follow-up was 7.2% in the propranolol group and 9.2% in the placebo group. **Conclusions**: In acute MI, propranolol reduced all-cause mortality, CV death, and sudden death from atherosclerotic heart disease.
COMMIT (β-Blocker)	Lancet 2005; 366:1622-1632	**Title**: Early Intravenous then Oral Metoprolol in 45,852 Patients with Acute Myocardial Infarction: randomised placebo-controlled trial Purpose: To evaluate the risks and benefits of incorporating early intravenous followed by oral metoprolol alongside standard therapies in a diverse group of patients. **Method**s: A study involving 45,852 patients admitted to hospitals within 24 h of suspected acute MI evaluated the effects of metoprolol versus placebo. Primary outcomes included a composite of cardiovascular death, reinfarction, or cardiac arrest, and death from any cause during the treatment period. **Results**: Allocation of metoprolol did not yield significant reductions in the co-primary outcomes. The occurrence of death, reinfarction, or cardiac arrest did not significantly differ between metoprolol (9.4%) and placebo (9.9%) groups (OR 0.96, 95% CI 0.90-1.01, p=0.1). However, metoprolol exhibited a lower risk of reinfarction (2.0% vs. 2.5%) and ventricular fibrillation (2.5% vs. 3.0%) per 1000 treated. Conversely, there was a higher incidence of cardiogenic shock (5.0% vs. 3.9%) (OR 1.30, 95% CI 1.19-1.41, p<0.00001). The overall impact varied over time, with an adverse effect in the early days and a beneficial effect thereafter. The net effect depended on patient stability, with a substantial hazard in haemodynamically unstable patients and moderate benefit in relatively stable patients (particularly after the initial days). **Conclusions**: Early β-blocker therapy in acute MI decreases reinfarction and ventricular fibrillation but increases cardiogenic shock risk, primarily within the first day.
ROOBY (CABG)	NEJM 2017;377:623-32	**Title**: Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass Purpose: Reporting of 5-yr outcomes in patients included in the Veterans Trial of on-pump vs. off-pump CABG. **Method**s: 2203 patients were randomly assigned to undergo either on-pump or off-pump CABG. The primary 5-yr outcomes were all-cause mortality and a composite of major CV events or non-fatal MI. **Results**: 5-yr mortality was 15.2% in the off-pump group, compared with 11.9% in the on-pump group (RR 1.28; 95% CI 1.03 to 1.58; P=0.02). The rate of major CV events in the off-pump group was 31.0% compared to 27.1% in the on-pump group (RR 1.14; 95% CI 1.00 to 1.30; P=0.046). **Conclusions**: Off-pump CABG led to lower rates of 5-yr survival and event-free survival when compared to on-pump CABG.
SYNTAX (CABG and PCI)	NEJM 2009;360:961-72	**Title**: Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease Purpose: Compare PCI and CABG for treating patients with previously untreated three-vessel or left main CAD. **Method**s: 1800 patients with three-vessel or left main coronary disease were randomized to CABG or PCI (1:1 ratio). The primary outcomes were a major adverse cardiac or cerebrovascular event. **Results**: Rates of primary outcomes at 12 mo were significantly higher in the PCI group (17.8% vs. 12.4%; P=0.002). At 12 mo, rates of death and MI were similar between groups and stroke was significantly more likely with CABG. **Conclusions**: CABG had a lower rate of major cardiac or cerebrovascular events, however the rate of stroke was increased with CABG whereas the rate of repeat revascularization was increased with PCI.

Trial Name	Reference	Clinical Trial Details
AMPLITUDE-O (GLP-1 Agonist)	NEJM 2021; 385: 896-907	**Title**: Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes Purpose: To understand the effect of an exendin-based GLP-1 receptor agonist, efpeglenatide, on cardiovascular and renal outcomes in patients with T2DM. **Method**s: Randomized, placebo-controlled trial across 28 countries in 344 sites. Participants were randomly allocated to receive either weekly subcutaneous injections of efpeglenatide or placebo. The primary focus was on the occurrence of the first major adverse cardiovascular event (MACE). **Results**: 4076 participants were enrolled. Among participants assigned to receive efpeglenatide, a composite renal outcome event, encompassing a decline in kidney function or the presence of macroalbuminuria, occurred in 353 individuals (13.0%). In contrast, among those assigned to receive placebo, 250 participants (18.4%) experienced the same outcome. Adverse effects such as diarrhea, constipation, nausea, vomiting, or bloating were more common with efpeglenatide compared to placebo. Conclusion: The administration of weekly subcutaneous injections of efpeglenatide resulted in a reduced risk of cardiovascular events compared to those who received a placebo.
HARMONY-OUTCOMES (GLP-1 Agonist)	Lancet 2018; 392: 1519-1529	**Title**: Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes): A Double-Blind, Randomized Placebo-Controlled Trial Purpose: To assess the safety and effectiveness of albiglutide in preventing cardiovascular death, myocardial infarction, or stroke. **Method**s: Double-blind, randomized, placebo-controlled trial in 28 countries with 610 sites. The primary outcome was the initial incidence of cardiovascular death, MI, or stroke, as assessed in the intention-to-treat population. **Results**: 4731 patients received albiglutide and 4732 patients received placebo. In the albiglutide group, the primary composite outcome was observed in 338 patients (7%) out of a total of 4731, with an incidence rate of 4.6 events per 100 person-years. In contrast, the placebo group had 428 patients (9%) out of 4732, with an incidence rate of 5.9 events per 100 person-years. Conclusion: Albiglutide demonstrated superiority over placebo in terms of major adverse cardiovascular events among patients diagnosed with both type 2 diabetes and cardiovascular disease.
LEADER (GLP-1 Agonist)	NEJM 2016;375:311-22	**Title**: Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes Purpose: To investigate the cardiovascular effects of liraglutide (GLP1 analogue) when added to standard care in patients with T2DM. **Method**s: 9340 patients with T2DM at high cardiovascular risk were randomly assigned to receive liraglutide or placebo. **Results**: The primary outcome (first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke) was observed in significantly less patients on liraglutide (13.0%) than placebo (14.9%) (hazard ratio, 0.87; 95% confidence interval, 0.78-0.97; P<0.001 for noninferiority; P=0.01 for superiority). Conclusion: In patients with T2DM, liraglutide reduced the rate of first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke.
PIONEER 6 (GLP-1 Agonist)	NEJM 2019; 381: 841-851	**Title**: Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes Purpose: To establish cardiovascular safety data for oral semaglutide. **Method**s: Event-driven, randomized, double-blind, placebo-controlled trial involving patients at high cardiovascular risk. **Results**: 3183 patients received either oral semaglutide or placebo through random assignment. Within the oral semaglutide group, 61 out of 1591 patients (3.8%) experienced major adverse cardiovascular events, while in the placebo group, 76 out of 1592 patients (4.8%) encountered such events. Conclusion: In patients with T2DM, cardiovascular risk profile of oral semaglutide was not inferior to that of the placebo.
REWIND (GLP-1 Agonist)	Lancet 2019;394:121-30	**Title**: Dulaglutide and Cardiovascular Outcomes in T2DM (REWIND): A Double-Blind, Randomized Placebo-Controlled Trial Purpose: To assess the effects of adding the GLP-1 receptor agonist dulaglutide to existing antihyperglycemic regimens on major cardiovascular events in patients with T2DM. **Method**s: 9901 patients with T2DM ≥50 years old with previous CVD or cardiovascular risk factors were randomly assigned to receive dulaglutide (1.5 mg weekly) or placebo. Primary composite outcome was first occurrence of non-fatal MI, non-fatal stroke, or death from cardiovascular causes. **Results**: Over a median follow-up of 5.4 years, patients treated with dulaglutide had a lower rate of the primary composite outcome compared to those on placebo (12.0% vs. 13.4%). However, there was no significant difference in all-cause mortality between the two groups. Conclusion: In middle-aged and older adults with T2DM with previous CVD or cardiovascular risk factors, dulaglutide could be considered for managing glycemic control.
SUSTAIN-6 (GLP-1 Agonist)	NEJM 2016; 375: 1834-1844	**Title**: Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes Purpose: To evaluate whether semaglutide is noninferior to placebo in terms of cardiovascular safety in patients diagnosed with type 2 diabetes. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. **Method**s: Randomized, double-blind, placebo-controlled, parallel-group trial in 20 countries at 230 sites. The primary outcome was the initial instance of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. **Results**: The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group. Conclusion: In high-risk type 2 diabetes patients, semaglutide showed significantly lower rates of cardiovascular death, myocardial infarction, or stroke compared to placebo.
COMPLETE (PCI)	NEJM 2019;381:1411-21	**Title**: Complete Revascularization with Multivessel PCI for Myocardial Infarction Purpose: To assess whether PCI of nonculprit lesions reduced rates of CV death or MI in STEMI patients. **Method**s: Patients with STEMI and successful PCI of culprit lesions were randomized to complete revascularization with PCI or no further revascularization. The primary outcome was a composite of CV death or MI. **Results**: At 3 yr, the primary outcome occurred in 7.8% of patients in the complete-revascularization group, compared with 10.5% in the culprit-lesion PCI only group (hazard ratio 0.74; 95% CI 0.60 to 0.91; P=0.004). The benefit was observed regardless of the intended timing of nonculprit lesion PCI. **Conclusions**: In patients with STEMI and multivessel CAD, complete revascularization by PCI further reduced the risk of CV death or MI as compared to culprit-lesion-only PCI.
COURAGE (PCI)	NEJM 2007;356:1503-16	**Title**: Optimal Medical Therapy with or without PCI for Stable Coronary Disease Purpose: Compare initial strategy of PCI plus intensive pharmacological therapy and lifestyle intervention against optimal medical therapy alone, in patients with stable coronary disease. **Method**s: 2287 patients with myocardial ischemia and significant CAD were randomized to PCI with optimal medical therapy, or optimal medical therapy alone. The primary outcome was all-cause mortality and non-fatal MI. **Results**: There were 211 primary events in the PCI group and 202 in the optimal medical therapy group (hazard ratio for PCI, 1.05; 95% CI 0.87 to 1.27; P=0.62). There were no significant differences between groups in the composite of death, MI, stroke, or hospitalizations for ACS. **Conclusions**: Compared with optimal medical therapy alone, PCI plus medical therapy did not reduce all-cause mortality and non-fatal MI, and it did not reduce the incidence of major CV events.
EXCEL (PCI)	NEJM 2019;381:1820-30	**Title**: Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease Purpose: Assess long-term outcomes after PCI with contemporary drug-eluting stents, as compared with CABG, in patients with left main CAD. **Method**s: 1905 patients with left main CAD of low/intermediate anatomical complexity were randomized to PCI or CABG. The primary outcome was a composite of death, stroke or MI. **Results**: At 5 yr, the primary outcome occurred in 22.0% of PCI patients and 19.2% of CABG patients (2.8% difference; 95% CI -0.9 to 6.5; P=0.13). Rates of CV death and MI were not significantly different between groups. All cerebrovascular events were less frequent after PCI than CABG (3.3% vs. 5.2%; 95% CI -3.8 to 0). **Conclusions**: Among patients with left main CAD, there was no significant difference between PCI and CABG in terms of the composite outcome of death, stroke, or MI at 5 yr .
MASS II (PCI, CABG, and medical therapy)	Circulation 2010;122:949-57	**Title**: Ten-Year Follow-Up Survival of the Medicine, Angioplasty, or Surgery Study (MASS II) Purpose: Compare 10-yr follow-up of PCI, CABG, and medical treatment in patients with multivessel coronary disease, UA, and preserved ventricular function. **Method**s: 611 patients were randomized to CABG, PCI, or medical treatment. The primary endpoints were overall mortality, Q-wave MI, or refractory angina requiring revascularization. **Results**: 10-yr survival was 74.9% with CABG, 75.1% with PCI, and 13.3% with medical treatment (P=0.089). 10-yr rates of MI were 10.3% with CABG, 13.3% with PCI, and 20.7% with medical treatment (P<0.010). 10-yr freedom from angina was 64% with CABG, 59% with PCI, and 43% with medical treatment (P<0.001). **Conclusions**: Compared to medical therapy, CABG resulted in greater relief of angina symptoms and lower rates of subsequent MI, additional revascularization, and cardiac death. Compared to PCI, CABG resulted in decreased need for further revascularization, a lower incidence of MI, and lower risk of combined events.

Trial Name	Reference	Clinical Trial Details
PRAMI (PCI)	NEJM 2013; 369:1115-1123	**Title**: Randomized Trial of Preventive Angioplasty in Myocardial Infarction Purpose: To determine whether incorporating preventive PCI into infarct artery treatment would decrease the overall occurrence of cardiac-related deaths, nonfatal MI, or persistent angina. **Method**s: 465 acute STEMI patients receiving infarct-artery PCI were randomized to preventive PCI or none. The primary endpoint was a composite of cardiac death, MI, or refractory angina. **Results**: The trial on preventive PCI was terminated early in January 2013 due to conclusive **results**. During a 23-month follow-up, patients receiving preventive PCI had significantly lower rates of the primary outcome compared to those without preventive PCI. **Conclusions**: Preventive PCI in non-infarct coronary arteries reduced adverse cardiovascular events compared to PCI limited to the infarct artery.
ODYSSEY OUTCOMES (PCSK9)	NEJM 2018;379:2097-107	**Title**: Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome Purpose: Determine whether alirocumab would improve CV events after ACS in patients receiving high-intensity statin therap.y **Method**s: 18924 patients receiving high-intensity statins for ACS 1-12 prior were randomized to alirocumab SQ at 75 mg or placebo, every 2 wk. The primary endpoint was a composite of death from CHD, non-fatal MI, fatal or non-fatal stroke, or UA **Results**: The primary endpoint occurred in 9.5% of patients in the alirocumab group and in 11.1% of patients in the .placebo group (hazard ratio 0.85; 95% CI 0.78 to 0.93; P<0.001). The incidence of adverse events was similar in the two groups. **Conclusions**: Among patients with ACS in the preceding 1-12 mo, use of alirocumab significantly reduces all-cause mortality and MI.
ACME (PCTA)	NEJM 1992;326:10-16	**Title**: A Comparison of Angioplasty with Medical Therapy in the Treatment of Single-Vessel Coronary Artery Disease Purpose: Compare the effects of percutaneous transluminal coronary angioplasty (PTCA) on angina and exercise tolerance in patients with stable single-vessel disease **Method**s: Patients with exercise-induced myocardial ischemia and epicardial artery stenosis were randomized to PTCA or medical therapy, and repeat exercise testing performed at 6 mo. **Results**: PTCA was successful in 80% of patients, reducing mean % stenosis from 76% to 36%. At 6 mo, 64% PTCA patients were angina-free, compared with 46% of medically treated patients. PTCA-treated patients had longer exercise durations (2.1 vs. 0.5 min, P<0.0001) than medically treated patients. **Conclusions**: PTCA offers earlier and better relief of angina than medical therapy in patients with single-vessel disease.
BARI 2D (Revascularization vs medical therapy)	NEJM 2009;360:2503-15	**Title**: A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease Purpose: Determine optimal treatment for patients with T2DM and stable ischemic heart disease. **Method**s: Patients with T2DM and heart disease were randomized to prompt revascularization with intensive medical therapy, or intensive medical therapy alone. Primary endpoints were mortality, MI, or stroke. **Results**: 5-yr survival did not differ significantly between groups (88.3% in revascularization group vs. 87.8% in the medical therapy group; P=0.97). In the PCI group, there were no significant differences in primary endpoints, while in the CABG group, rates of CV events were significantly lower with revascularization than medical therapy (22.4% vs. 30.5%; P=0.01). **Conclusions**: There was no significant difference in the rates of death and major CV events between prompt revascularization and medical therapy.
CANVAS (SGLT2 Inhibitors)	NEJM 2017;377:644-57	**Title**: Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes Purpose: To assess the effects of canagliflozin on cardiovascular, renal, and safety outcomes in patients with T2DM. **Method**s: 10142 patients with T2DM at high cardiovascular risk were randomly assigned to receive canagliflozin or placebo. Primary outcome was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. **Results**: In comparison to placebo, canagliflozin showed significantly lower rates of the primary outcome (26.9 vs. 31.5 participants per 1000 patient-years). However, canagliflozin was associated with a higher risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years). Conclusion: Canagliflozin lowered the risk of cardiovascular events but increased the risk of amputation in patients with T2DM at high cardiovascular risk.
DECLARE-TIMI 58 (SGLT2 Inhibitors)	NEJM 2019;380:347-57	**Title**: Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes Purpose: To assess the safety and efficacy of the SGLT2i dapagliflozin in patients with T2DM who had or were at risk for ASCVD. **Method**s: 17160 patients were randomly assigned to receive 10 mg dapagliflozin daily or placebo. Primary composite safety outcome was MACE (major adverse cardiovascular events), defined by cardiovascular death, MI, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. **Results**: In terms of safety, dapagliflozin was found to be noninferior to placebo. In terms of efficacy, dapagliflozin was associated with a lower rate of cardiovascular death or hospitalization for heart failure compared to placebo. However, it did not significantly reduce rates of major adverse cardiovascular events (MACE). Conclusion: Dapagliflozin was noninferior to placebo with respect to MACE but was associated with lower rates of cardiovascular death or hospitalization for heart failure in patients with T2DM who had or were at risk for ASCVD.
EMPA-REG OUTCOME (SGLT2 Inhibitors)	NEJM 2015;373:2117-28	**Title**: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Purpose: To investigate the effects of empagliflozin on cardiovascular morbidity and mortality in patients with T2DM at high cardiovascular risk. **Method**s: 7020 patients were randomly assigned to receive empagliflozin (10 mg or 25 mg) or placebo daily. **Results**: Risk of hospitalization from heart failure, death from any cause, or cardiovascular causes was significantly lower in the pooled empagliflozin group as compared to placebo. There were no significant differences in the rates of MI or stroke. There were increased rates of genital infection with empagliflozin. Conclusion: Empagliflozin reduced rates of death from any cause and death from CVD in patients with T2DM at high risk for cardiovascular events.
IMPROVE-IT (Selective cholesterol absorption inhibitor and statin)	NEJM 2015;372:2387-97	**Title**: Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes Purpose: Assess the effects of adding ezetimibe to statin therapy in reducing the rate of CV events. **Method**s: 18144 patients who were hospitalized with ACS were randomized to combination (simvastatin 40 mg plus ezetimibe 10 mg), simvastatin 40 mg alone, or placebo. Primary endpoint was a composite of CV death, non-fatal MI, UA, or non-fatal stroke. **Results**: The Kaplan-Meier event rates for the primary endpoint were 32.7% in the combination group and 34.7% in the statin monotherapy group (P<0.001). Rates of pre-specified muscle, gallbladder, and hepatic adverse effects were similar. **Conclusions**: Ezetimibe added to statin reduces mortality in ACS patients.
CARE (Statin)	NEJM 1996;335:1001-09	**Title**: The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels Purpose: Determine the effects of cholesterol-lowering in patients with coronary disease and average cholesterol levels. **Method**s: Patients with MI who had plasma cholesterol levels <240 mg were administered either 40 mg pravastatin or placebo. The primary endpoint was a fatal coronary event or fatal MI. **Results**: The primary endpoint occurred in 10.2% of the pravastatin-treated patients and 13.2% of placebo-treated patients (95% CI 9% to 36%; P=0.003). There were no significant differences in overall mortality or mortality from nonvascular causes. Pravastatin lowered the rate of coronary events more among men than women. **Conclusions**: Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol.
PROVE IT – TIMI 22 (Statin)	NEJM 2004;350:1495-504	**Title**: Intensive vs. Moderate Lipid Lowering with Statins after Acute Coronary Syndromes Purpose: Determine the optimal LDL-C level in patients undergoing statin therapy for reduction in risk of CV events. **Method**s: 4162 patients hospitalized with ACS in the preceding 10 d were assigned to pravastatin 40 mg daily or atorvastatin 80 mg daily. The primary end point was a composite of all-cause mortality MI, UA, revascularization, and stroke. **Results**: Event rates were 26.3% in the pravastatin group and 22.4% in the atorvastatin group (P=0.005; 95% CI 5 to 26%). The study established the superiority of the more intensive regimen. **Conclusions**: In patients hospitalized for ACS, high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin.
TNT (Statin)	NEJM 2005;352:1425-35	**Title**: Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease Purpose: Assess the efficacy and safety of LDL-lowering below 100 mg/dL in patients with stable CHD. **Method**s: 10001 patients with stable CHD and LDL <130 mg/dL were randomized to double blind therapy of atorvastatin 10 mg or 80 mg daily. The primary endpoint was the occurrence of a first major CV event. **Results**: A primary endpoint occurred in 8.7% of patients treated with atorvastatin 80 mg, as compared with 10.9% in patients receiving atorvastatin 10 mg. There was no difference in overall mortality between groups. **Conclusions**: Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d.

Trial Name	Reference	Clinical Trial Details
TRANSCATHETER AORTIC VALVE REPLACEMENT		
PARTNER II	NEJM 2016;374:1609-20	**Title**: Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients Purpose: Evaluate survival rates between TAVR and surgical aortic valve replacement, in intermediate risk patients. **Method**s: 2032 intermediate risk patients were randomized to TAVR or surgical replacement. The primary endpoint was all-cause mortality or disabling stroke at 2 yr. **Results**: The rates of primary outcomes were similar between TAVR and surgical replacement groups (P=0.001). At 2 yr, the Kaplan-Meier event rates were 19.3% in the TAVR group and 21.1% in the surgical group (hazard ratio 0.89; 95% CI 0.73 to 1.09; P=0.25). Surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitation. **Conclusions**: In intermediate-risk patients with AS, TAVR and SAVR resulted in similar rates of all-cause mortality and disabling stroke.
PARTNER III	NEJM 2019;380:1695-705	**Title**: Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients Purpose: Compare major outcomes in low-risk patients between TAVR and surgical aortic-valve replacement. **Method**s: 1000 patients with severe aortic stenosis and low surgical risk were randomized to TAVR or surgical aortic valve replacement. The primary endpoint was a composite of death, stroke, or rehospitalization at 1 yr. **Results**: The Kaplan-Meier event rates were significantly lower in the TAVR group than the surgery group (8.5% vs. 15.1%; 95% CI -10.8 to -2.5; P<0.001). At 30 d, TAVR resulted in lower stroke rates and new-onset atrial fibrillation. There were no significant differences in major vascular complications, new pacemaker insertion, or paravalvular regurgitation. **Conclusions**: Among low-surgical risk patients with severe AS, the rate of the composite of death, stroke, or rehospitalization was significantly lower with TAVR compared to surgical aortic-valve replacement.
HEART FAILURE		
COAPT	NEJM 2018;379:2307-18	**Title**: Transcatheter Mitral-Valve Repair in Patients with Heart Failure Purpose: Assess improvement in outcomes in patients with MR due to LV dysfunction, from transcatheter mitral valve repair. **Method**s: Patients with HF and secondary mitral regurgitation were randomized to transcatheter mitral-valve repair plus medical therapy, or to medical therapy alone. The primary endpoint was hospitalization for HF at 24 mo. **Results**: The primary endpoint was 35.8% in the intervention group, compared to 67.9% in the control group (hazard ratio 0.53; 95% CI 0.40 to 0.70; P<0.001). Death from any cause occurred at 29.1% in the intervention group compared with 46.1% in the control group (hazard ratio 0.62; 95% CI 0.46 to 0.82; P<0.001). **Conclusions**: Among patients with HF and secondary MR who remained symptomatic despite medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for HF and lower mortality than medical therapy alone.
CHARM	Lancet 2003;362:759-66	**Title**: Effects of Candesartan on Mortality and Morbidity in Patients with Chronic Heart Failure: The Charm-Overall Programme Purpose: Determine whether ACEI use could reduce mortality and morbidity in patients with CHF. **Method**s: Patients with LVEF <40% not receiving ACEIs were randomized to candesartan or placebo. The primary outcome was all-cause mortality, CV death, or hospital admission for CHF. **Results**: Mortality was 23% in the candesartan group and 25% in the placebo group (hazard ratio 0.91; 95% CI 0.83 to 1.00; P=0.055), with fewer CV deaths (18% vs. .20%; P=0.012). **Conclusions**: Candesartan reduced overall mortality, CV death, and CHF hospitalizations.
CIBIS II	Lancet 1999;353:9-13	**Title**: The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial Purpose: Investigate the efficacy of bisoprolol in decreasing all-cause mortality in CHF. **Method**s: 2647 patients with LVEF <35% receiving standard therapy were randomized to bisoprolol or placebo. The primary outcome was all-cause mortality. **Results**: All-cause mortality was significantly lower with bisoprolol than placebo (11.8% vs. 17.3%, hazard ratio 0.66; 95% CI 0.54 to 0.81; P<0.0001). Treatment effects were independent of etiology or severity of HF/ **Conclusions**: Bisoprolol reduced all-cause mortality, CV death, all-cause hospitalization, and CHF hospitalization/
COMET	Lancet 2003;362:7-13	**Title**: Comparison of Carvedilol and Metoprolol on Clinical Outcomes in Patients with Chronic Heart Failure in the Carvedilol or Metoprolol European Trial (Comet): Randomised Controlled Trial Purpose: Compare outcomes of chronic HFrEF patients on carvedilol or metoprolol. **Method**s: 1511 patients with CHF were randomized to carvedilol 25 mg twice daily, and 1518 randomized to metoprolol 50 mg twice daily. The primary endpoints were all-cause mortality, and the composite of all-cause mortality or all-cause admissio.n **Results**: The all-cause mortality was 34% for carvedilol patients and 40% for metoprolol patients (hazard ratio 0.83; 95% CI 0.74 to 0.93; P=0.0017). Incidence of side effects and withdrawal did not differ significantly between groups. **Conclusions**: Carvedilol was associated with a reduction in all-cause mortality compared with metoprolol.
COPERNICUS	NEJM 2001;344:1651-58	**Title**: Effect of Carvedilol on Survival in Severe Chronic Heart Failure Purpose: Assess the effects of β-blockade on hospitalization and mortality in patients with severe HF. **Method**s: 2289 patients with HF symptoms at rest and an EF <25% were randomized to carvedilol or placebo. Primary endpoints were rates of hospitalization and mortality. **Results**: There was a 35% reduction in mortality risk in patients treated with carvedilol than placebo (95% CI 19% to 48%; P=0.0018). **Conclusions**: Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF.
DAPA-HF	NEJM 2019;381:1995-2008	**Title**: Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction Purpose: Assess the efficacy of the SGLT2 inhibitor dapagliflozin in patients with HFrEF, independent of T2DM status. **Method**s: 4744 patients with HF and EF <40% were randomized to receive dapagliflozin 10 mg once daily, or placebo, in addition to recommended therapy. The primary outcome was worsening HF or CV death. **Results**: The primary outcome occurred in 16.3% of dapagliflozin-treated patients and 21.2% of placebo patients (hazard ratio 0.74; 95% CI 0.65 to 0.85; P<0.001). A worsening of HF occurred at 10.0% in the dapagliflozin group and 13.7% in the placebo group (hazard ratio 0.70; 95% CI 0.59 to 0.83). Findings in patients with DM were comparable to those in patients without DM. **Conclusions**: In patients with HFrEF, the risk of worsening HF or death from CV causes was lower among those who received dapagliflozin than those who received placebo.
DELIVER	NEJM 2022;387:1089-1098	**Title**: Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction Purpose: Assess the efficacy of SGLT2 inhibitor dapagliflozin in patients with HFpEF or mildly reduced EF, independent of T2DM status **Method**s: 6263 patients with HF and EF >40% were randomized to receive dapagliflozin 10 mg once daily, or placebo, in addition to recommended therapy. The primary outcome was worsening HF or CV death. **Results**: The primary outcome occurred in 16.4% of dapagliflozin-treated patients and 19.5% of placebo-treated patients (hazard ratio, 0.82; 95% CI 0.73 to 0.92; P<0.001). Worsening of HF occurred at 11.8% in the dapagliflozin group and 14.5% in the placebo group (hazard ratio 0.79; 95% CI 0.69 to 0.91). Findings in patients with EF >60% and EF <60% were comparable. Findings in patients with DM were comparable to those in patients without DM. **Conclusions**: In patients with HF and EF >40%, dapagliflozin reduced the risk of worsening HF or CV death.
EMPEROR-Preserved	NEJM 2021;385:1451-1461	**Title**: Empagliflozin in Heart Failure with a Preserved Ejection Fraction Purpose: Assess the efficacy of the SGLT2 inhibitor empagliflozin in patients with HFmrEF and HFpEF, irrespective of diabetes status. **Method**s: 5988 patients with symptomatic HF and an EF >40% were randomized to receive empagliflozin 10 mg once daily, or placebo, in addition to usual therapy. The primary outcome was a composite of CV mortality or hospitalization for HF. **Results**: Empagliflozin was associated with a lower risk of CV mortality or hospitalization for HF (13.8% vs.17.1%; HR 0.79; 95% CI 0.69 to 0.90; P<0.001), which was mainly related to fewer HF hospitalization events in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. **Conclusions**: In patients with HFmrEF and HFpEF, empagliflozin was associated with a lower risk of the CV mortality or hospitalization for HF, and this effect was primarily driven by fewer HF hospitalizations.
EMPEROR-Reduced	NEJM 2020;383:1413-1424	**Title**: Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure Purpose: Assess the efficacy of the SGLT2 inhibitor empagliflozin in patients with HFrEF, irrespective of diabetes status. **Method**s: 3730 patients with symptomatic HF and an EF <40% were randomized to receive empagliflozin 10 mg once daily, or placebo, in addition to usual therapy. The primary outcome was a composite of CV mortality or hospitalization for worsening HF. **Results**: Empagliflozin was associated with a lower risk of CV mortality or hospitalization for HF (19.4% vs. 24.7%; HR 0.75; 95% CI 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of diabetes status. **Conclusions**: In patients with HFrEF, empagliflozin was associated with a lower risk of CV mortality or hospitalization for HF, independent of diabetes status.

Trial Name	Reference	Clinical Trial Details
I-PRESERVE	NEJM 2008;359:2456-67	**Title**: Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction Purpose: Study the effects of irbesartan in patients with HF and EF >45%. **Method**s: 4128 patients with HF and EF >45% were randomized to irbesartan 300 mg daily, or matching placebo. The primary outcome was a composite of all-cause mortality or CV hospitalization. **Results**: The primary outcome occurred in 742 patients in the irbesartan group and 763 placebo patients (hazard ratio 0.95; 95% CI 0.86 to 1.05; P=0.35). Overall, rates of death were 52.6 and 52.3 per 1000-patient-yr, respectively. **Conclusions**: In patients with CHF and normal LVEF, treatment with ARB (irbesartan) did not improve mortality or CV morbidity compared to placebo.
PARADIGM-HF	NEJM 2014;371:993-1004	**Title**: Angiotensin–Neprilysin Inhibition vs. Enalapril in Heart Failure Purpose: Compare survival in HFrEF patients treated with enalapril or an angiotensin-neprilysin inhibitor. **Method**s: 8442 patients with HF and EF <40% were randomized to LCZ696 200 mg twice daily, or enalapril 10 mg twice daily. The primary endpoint was a composite of CV death and HF hospitalization. **Results**: The primary outcome occurred in 21.8% of LCZ696-treated patients and 26.5% of enalapril patients (hazard ratio 0.80; 95% CI 0.73 to 0.87; P<0.001). 13.3% and 16.5% of patients treated with LCZ696 and enalapril, respectively, died of CV causes (hazard ratio 0.80; 95% CI 0.71 to 0.89; P<0.001.) **Conclusions**: Novel drug (LCZ696) containing valsartan and a neprilysin inhibitor (prevents degradation of natriuretic peptides) reduces hospitalization and mortality.
PRESERVED-HF	Nature 2021; 27: 1954-1960	**Title**: The SGLT2 iInhibitor Dapagliflozin in Heart Failure with Preserved Ejection Fraction: A Multicenter Randomized Trial Purpose: To determine if treatment with SGLT2 inhibitor dapagliflozin will improve symptoms, physical limitations, and exercise function in patients with and without T2DM **Method**s: Randomized, multicentre trial. 324 patients were randomized to receive dapagliflozin or placebo. **Results**: The impact of dapagliflozin on multiple endpoints, including Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS), 6-minute walk test (6MWT), KCCQ Overall Summary Score (KCCQ-OS), weight, natriuretic peptides, glycated hemoglobin, and blood pressure, was assessed in a trial with 324 randomized patients. **Results**: Dapagliflozin demonstrated improvements in KCCQ-CS, physical limitations scores, 6MWT, KCCQ-OS, proportion of participants with meaningful improvements in KCCQ-OS, and weight reduction. No significant differences were observed in other secondary endpoints. Adverse events were comparable between dapagliflozin and placebo groups. **Conclusions**: After 12 wk of treatment with dapagliflozin, there was a significant improvement reported by patients in symptoms, physical limitations, and exercise function.
RALES	NEJM 1999;341:709-17	**Title**: The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure Purpose: Assess the efficacy of spironolactone on morbidity and mortality in patients with severe HF. **Method**s: 1663 patients with severe HF and LVEF <35% who were being treated with ACEI, loop diuretic and digoxin, were randomized to spironolactone 25 mg daily or placebo. The primary endpoint was all-cause mortality. **Results**: There was a mortality rate of 46% in the placebo group, compared to 35% in the spironolactone group (RR 0.70; 95% CI 0.60 to 0.82; P<0.001). The frequency of hospitalization for worsening HF was 35% less in the intervention group (RR 0.65l 95% CI 0.54 to 0.77, P<0.001). **Conclusions**: In severe CHF (class III/IV) and LVEF <35%, spironolactone reduced all-cause mortality, sudden death, and death due to progression of HF.
SCD-HeFT	NEJM 2005;352:225-37	**Title**: Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure Purpose: Study prognosis differences in CHF patients treated with amiodarone or ICD. **Method**s: 2521 patients with CHF and LVEF <35% were randomized to conventional therapy plus placebo, conventional therapy plus amiodarone, or conventional therapy plus shock-only single-lead ICD. The primary endpoint was death from any cause. **Results**: Mortality rates were 29% in placebo patients, 28% in the amiodarone group, and 22% in the ICD group (hazard ratio 1.06; 97.5% CI 0.86 to 1.30; P=0.53). ICD was associated with a decreased risk of death of 23% compared to placebo (hazard ratio 0.77; 97.5% CI 0.62 to 0.96; P=0.007). **Results** did not vary based on ischemic or nonischemic causes of CHF. **Conclusions**: In mild-to-moderate CHF, shock-only ICD significantly reduces risk of death; amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF.
TRACE	NEJM 1995;333:1670-76	**Title**: A Clinical Trial of the Angiotensin-Converting–Enzyme Inhibitor Trandolapril in Patients with Left Ventricular Dysfunction after Myocardial Infarction Purpose: Determine whether the mortality benefit of ACEI post-MI extends to all patients, or only selected patients. **Method**s: On d 3-7 post-MI, 1749 patients were randomized to receive oral trandolapril or placebo. The primary endpoint was all-cause mortality. **Results**: The mortality rate was 34.7% in the trandolapril group, compared with 42.3% in the placebo group (P=0.001; RR 0.78; 95% CI 0.67 to 0.91). Trandolapril reduced rates of sudden death (RR 0.75; 95% CI 0.59 to 0.98; P=0.03) and CV death (RR 0.75; 0.62 to 0.89; P=0.001). **Conclusions**: In patients with LV dysfunction post-MI, long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death.
ARRHYTHMIA		
AFFIRM	NEJM 2002;347:1825-33	**Title**: A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation Purpose: Compare rate and rhythm control in patients with AFib and high risk of stroke or death. **Method**s: 4060 patients with AFib were randomized to rhythm-control therapy with antiarrhythmic drugs, or rate-control therapy. **Results**: The mortality rate was 23.8% in rhythm-controlled patients and 21.3% in rate-controlled patients (hazard ratio 1.15; 95% CI 0.99 to 1.34; P=0.08). More patients were hospitalized in the rhythm-control group, with higher rates of adverse drug events. **Conclusions**: No significant difference in mortality rates between rate or rhythm control of AFib.
ARISTOTLE	NEJM 2011;365:981-92	**Title**: Apixaban vs. Warfarin in Patients with Atrial Fibrillation Purpose: Assess the efficacy of apixaban for stroke prevention in patients with AF, in comparison with warfarin. **Method**s: 18201 patients with AFib and one additional RF for stroke were randomized to apixaban 5 mg twice daily or warfarin. The primary outcome was stroke or systemic embolism. **Results**: The rate of primary outcome was 1.27% per year in the apixaban group and 1.60% per year in the warfarin group (hazard ratio 0.79; 95% CI 0.66 to 0.95; P<0.001). The rate of major bleeding was 2.13% per year with apixaban and 3.09% per year with warfarin (hazard ratio 0.69; 95% CI 0.69 to 0.80; P<0.001). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group and 0.47% per year in the warfarin group. **Conclusions**: AFib patients treated with apixaban had a lower incidence of stroke, major bleeding and mortality compared to warfarin.
AUGUSTUS	NEJM 2019;380:1509-24	**Title**: Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation Purpose: Elucidate benefits of antithrombotic regimens for patients with AFib and either ACS or previous PCI. **Method**s: Patients with AFib and a prior ACS or PCI were randomized to apixaban or a vitamin K antagonist, and to ASA or placebo for 6 mo. The primary outcome was major or clinically relevant non-major bleeding. **Results**: The primary outcome occurred in 10.5% of apixaban patients and 14.7% of vitamin K antagonist-patients (hazard ratio 0.69; 95% CI 1.59 to 2.25; P<0.001). Patients in the apixaban group had a lower incidence of death or hospitalization compared to the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio 0.83; 95% CI 0.74 to 0.93; P=0.002). **Conclusions**: In patients with AFib and recent ACS or PCI, apixaban reduced bleeding compared to regimens that included a vitamin K antagonist, ASA, or both.
COACT	JAMA Cardiol. 2020;5:1358-65	**Title**: Coronary Angiography after Cardiac Arrest without ST Segment Elevation: One-Year Outcomes of the COACT Randomized Clinical Trial Purpose: Compare 1-yr clinical outcomes of immediate angiography and PCI versus delayed angiography in resuscitated cardiac arrest patients without STEMI. **Method**s: 552 patients who had undergone cardiac arrest in the absence of STEMI were randomized to immediate coronary angiography, or angiography after recovery of neurological function. PCI was carried out as indicated by angiography, in keeping with the time allotments between groups. The primary endpoints were survival, MI, revascularization, hospitalization for HF, and the composite of death and MI, at 1 yr follow-up time. **Results**: Survival at 1-yr follow-up were 61.4% and 64.0% in the immediate angiography and delayed angiography groups, respectively (OR 0.90; 95% CI 0.63 to 1.28; P=0.51). Similar to 90-d outcomes, this represents a statistically insignificant difference. MI rates were 0.8% and 0.4% in the immediate and delayed groups, respectively (OR 1.96; 95% CI 0.18 to 21.8). The composite outcome of death, revascularization, or MI occurred at a rate of 42.9% and 40.6% in the immediate and delayed groups, respectively (OR 1.10; 95% CI 0.77 to 1.56). **Conclusions**: Similar to the previous 90-d follow-up, immediate angiography did not significantly improve 1-yr clinical outcomes compared to delayed angiography in resuscitated cardiac arrest patients without evidence of STEMI.

Trial Name	Reference	Clinical Trial Details
ENGAGE AF-TIMI48	NEJM 2013;369:2093-104	**Title**: Edoxaban vs. Warfarin in Patients with Atrial Fibrillation Purpose: Compare the long-term efficacy and safety of edoxaban and warfarin in AFib patients. **Method**s: 21105 patients with moderate-high risk AFib were randomized to two once-daily regimens of edoxaban or warfarin. The primary endpoint was stroke or systemic embolism. **Results**: The primary endpoint rate was 1.50% with warfarin and 1.18% in the edoxaban group (hazard ratio 0.79; 97.5% CI 0.63 to 0.99; P<0.001). The annualized rate of major bleeding was 3.43% with warfarin and 2.75% with high-dose edoxaban (hazard ratio 0.80; 95% CI 0.71 to 0.91; P<0.001). **Conclusions**: AFib patients treated with edoxaban had similar rates of stroke and lower rates of major bleeding compared to warfarin.
ETOH-AFib	NEJM 2020;382:20-28	**Title**: Alcohol Abstinence in Drinkers with Atrial Fibrillation Purpose: Study the effects of alcohol abstinence on secondary prevention of atrial fibrillation. **Method**s: Adults who consumed >10 standardized drinks/wk with AFib were randomized to abstinence or continuation of current practices. The two primary endpoints were freedom from AFib recurrence and total AFib burden. **Results**: After a 2-wk blanking period, AFib recurred in 53% of patients in the abstinence group and 73% of patients in the control group (hazard ratio 0.55; 95% CI 0.36 to 0.84; P=0.005). The AFib burden after 6 mo was lower in the abstinence group than the control group. **Conclusions**: Abstinence from alcohol reduced arrhythmia recurrences in regular drinkers with AFib.
RE-LY	NEJM 2009;361:1139-51	**Title**: Dabigatran vs. Warfarin in Patients with Atrial Fibrillation Purpose: Compare the reduction of stroke risk in AFib patients with warfarin versus dabigatran. **Method**s: 18113 patients with AFib and stroke risk were randomized to fixed doses of dabigatran (110 mg or 150 mg twice daily) or warfarin. The primary outcome was systemic embolism. **Results**: Rates of primary outcomes were 1.69% per year with warfarin, compared with 1.53% per year with 110 mg dabigatran (RR 0.91; 95% CI 0.74 to 1.11; P<0.001) and 1.11% per year with 150 mg dabigatran (RR 0.66; 95% CI 0.53 to 0.82; P<0.001). The rate of major bleeding was 3.36% in the warfarin group, compared to 2.71% in the dabigatran 110 mg group and 3.11% in the dabigatran 150 mg group. **Conclusions**: AFib patients treated with dabigatran had a lower incidence of stroke compared to warfarin, with similar rates of major bleeding.
ROCKET-AFib	NEJM 2011;365:883-91	**Title**: Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation Purpose: Compare rivaroxaban with warfarin in reducing stroke risk in AFib patients. **Method**s: 14264 patients with nonvalvular AFib were randomized to rivaroxaban 20 mg daily or dose-adjusted warfarin. The primary endpoint was stroke or systemic embolism. **Results**: The primary endpoint occurred in 1.7% of patients in the rivaroxaban group and 2.2% of patients on warfarin (hazard ratio 0.79; 95% CI 0.66 to 0.96; P<0.001). Major and non-major bleeding occurred in 14.9% of patients in the rivaroxaban group and 14.5% of warfarin patients (hazard ratio 1.03; 95% CI 0.96 to 1.11; P=0.44). **Conclusions**: In patients with AFib, rivaroxaban is non-inferior to warfarin for stroke prevention without an excess of major bleeding.
HYPERTENSION		
HYVET	NEJM 2008;358:1887-98	**Title**: Treatment of Hypertension in Patients 80 Years of Age or Older Purpose: Assess antihypertensive therapy for stroke risk reduction, in patients >80 yr with hypertension. **Method**s: 3845 patients with sBP >160 mmHg and >80 yr were randomized to indapamide SR 2.5 mg or placebo. Perindopril 2 mg or 4 mg was added if needed to achieve target BP 150/80 mmHg. The primary endpoint was fatal or non-fatal stroke. **Results**: Active treatment was associated with a 30% reduction in fatal or non-fatal stroke (95% CI -1 to 51; P=0.06), a 39% reduction in death from stroke (95% CI 1 to 62; P=0.05) and a 21% reduction in all-cause mortality (95% CI 4 to 35; P=0.02). **Conclusions**: In hypertensive patients >80 yr, treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non-fatal stroke.
SPRINT	NEJM 2015;373:2103-16	**Title**: A Randomized Trial of Intensive vs. Standard Blood-Pressure Control Purpose: Determine appropriate targets for sBP to reduce CV morbidity and mortality among patients without DM. **Method**s: 9361 patients with an sBP 130 mmHg or greater and increased CV risk, without diabetes, were randomized to sBP target <120 mmHg or <140 mmHg. The primary outcome was a composite of MI, other ACS, stroke, HF, or CV death. **Results**: There was a significant reduction in the rates of primary outcome in the intensive group compared to the conservative group (1.65% vs. 2.19%; hazard ratio 0.75; 95% CI 0.64 to 0.89; P<0.001). All-cause mortality was significantly lowered in the intensive group (hazard ratio 0.73; 95% CI 0.60 to 0.90; P=0.003). **Conclusions**: In patients with high risk of CV events excluding DM, strict sBP control (<120 mmHg) is associated with fewer CV events and lower all-cause mortality.
VALUE	Lancet 2004;363:2022-31	**Title**: Outcomes in Hypertensive Patients at High Cardiovascular Risk Treated with Regimens Based on Valsartan or Amlodipine: The Value Randomised Trial Purpose: Determine whether valsartan would reduce cardiac morbidity more than amlodipine in hypertensive patients with high CV risk. **Method**s: 15245 patients with hypertension and high CV risk were randomized to valsartan or amlodipine. The primary endpoint was a composite of cardiac morbidity and mortality. **Results**: The primary composite endpoints occurred in 10.6% of patients in the valsartan group and 10.4% of patients in the amlodipine group (hazard ratio 1.04; 95% CI 0.94 to 1.15; P=0.49). **Conclusions**: The valsartan group had a higher incidence of MI than the amlodipine group.

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CP Clinical Pharmacology

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Acronyms

ACE	angiotensin converting enzyme	cGMP	cyclic guanosine monophosphate	INR	international normalized ratio	PK	pharmacokinetics
ACh	acetylcholine			MME	milligram morphine equivalents	SLC	solute carrier
ADE	adverse drug event	Cl	clearance rate	NDC	National Drug Code	SSRI	selective serotonin reuptake inhibitor
ADME	absorption, distribution, metabolism, and excretion	COMT	catechol-O-methyltransferase	NE	norepinephrine (NPN)		
		CSF	cerebrospinal fluid	NPO	nothing by mouth (nil per os)	TBW	total body water
ADR	adverse drug reaction	CYP	cytochrome P450 enzyme	NS	nervous system	TDM	therapeutic drug monitoring
ARB	angiotensin receptor blocker	DIN	drug identification number	$P_{o/w}$	partition coefficient of a drug	TI	therapeutic index
AUC	area under the concentration-time curve	FDA	Food and Drug Administration	PD	pharmacodynamics	Vd	volume of distribution
		GFR	glomerular filtration rate	PDE	phosphodiesterase		
BBB	blood-brain barrier	HH	Henderson-Hasselbalch	P-gp	P-glycoprotein		

General Principles

Drug Nomenclature

- **DIN or NDC:** Drug Identification Number assigned to each drug approved by Health Canada; National Drug Code assigned by FDA (US), equivalent to the DIN in Canada
- **DIN-HM:** identification number assigned to registered homeopathic products in Canada
- **NPN:** Natural Product Number; refers to natural health products (excluding homeopathic medicines) regulated by the Natural and Non-Prescription Health Products Directorate (NNHPD) within Health Canada
- **chemical name:** describes chemical structure; consistent in all countries via International Union of Pure and Applied Chemistry (IUPAC) (e.g. N-(4-hydroxyphenyl)acetamide = acetaminophen)
- **non-proprietary (generic) name:** approved name (requires approval from nomenclature committee), official name (listed in pharmacopeia), often referred to as the generic name; may contain an ending similar to drugs in its class (e.g. atorvastatin, pravastatin, simvastatin)
- **proprietary (trade) name:** the brand name or registered trademark (e.g. Lipitor®)

Phases of Clinical Drug Testing

- pre-clinical: assessments of the drug before it is given to humans (e.g. laboratory studies in cells, tissues, organs, or animals) to examine PK and PD properties and potential toxicities
- phase I: first administration of the drug to a small number of healthy volunteers, following preclinical studies; to explore PK and safety
- phase II: first administration of the drug to patients, small sample sizes; primarily to determine efficacy, safety, dose range, and PK
- phase III: comparative studies (new drug vs. placebo or standard of care) to establish safety and efficacy in a larger group of patients; generally involves double-blinded RCTs
- phase IV: post-marketing surveillance, wider distribution; to determine effectiveness (in contrast to efficacy), monitor long-term drug effects, and detect previously unappreciated ADRs

Drug Administration

- choice of route of administration depends on available formulations, local and systemic effects, desired time to onset and/or duration of action, adherence, and other patient characteristics

Table 1. Routes of Drug Administration

Route	Advantage	Potential Disadvantages
Oral (PO)	Convenient, easy to administer Large surface area for absorption Inexpensive relative to parenteral administration	Incomplete absorption Hepatic and/or intestinal first-pass effects Adverse GI effects Higher likelihood of drug-drug/drug-food interactions May be affected by dietary factors Requires an intact GI system Affected by GI motility
Buccal/Sublingual (SL)	Rapid onset of action No intestinal/hepatic first-pass effect	Must be lipid-soluble, non-irritating
Rectal (PR)	Smaller hepatic first-pass effect than with oral Use when NPO, vomiting, or unconscious	Inconvenient Irritation at site of application Erratic absorption Appropriate for limited number of drugs
Intravenous (IV)	No first-pass effect Provides rapid onset of action Easy to titrate dose	Little ability to undo inappropriate drug administration Risk of infection, bleeding, vascular injury, and extravasation More expensive Requires sterile conditions and trained professionals
Intramuscular (IM)	Depot storage if oil-based = slow release of drug Aqueous solution = rapid onset of action (e.g. epinephrine for serious allergic reactions)	Pain/hematoma at site of injection Requires sterile conditions
Subcutaneous (SC)	Constant, even absorption Alternative to IV Easier administration (can be self-administered)	Pain at site of injection Generally smaller volumes than IM Possible tissue damage from multiple injections
Intrathecal	Directly into CSF Bypasses BBB and blood-CSF barrier	Risk of infection and CSF leak Requires sterile conditions and trained personnel Invasive procedure
Inhalation	Immediate action in lungs Rapid delivery to blood No hepatic first-pass effect and generally less presystemic clearance	Inhalation can cause irritant effects on airways such as stimulation of the cough reflex
Topical (skin, mucous membranes, eyes)	Easy to administer Localized (limited systemic absorption)	Effects are generally limited to site of application
Transdermal	Drug absorption through intact skin, easy to apply No intestinal/hepatic first-pass effect	Irritation at site of application Delayed onset of action
Others (Intraperitoneal, Intra-articular)	Local effect	Risk of infection and hemorrhage Requires sterile conditions and trained personnel

Pharmacokinetics

- "what the body does to the drug" – i.e. the fate of a drug in the body following administration
- **definition:** the time-course of drug absorption, distribution, metabolism, and excretion from the body following drug administration

Absorption

- **definition**: movement of the drug from the site of administration into bloodstream

Mechanisms of Drug Absorption

- most drug absorption involves passive diffusion
- other mechanisms include active transport, facilitated diffusion, and pinocytosis/phagocytosis

Factors Affecting the Rate and Extent of Drug Absorption

- **lipophilicity** ($P_{o/w}$)
- local blood flow at the site of administration (e.g. sublingual vessels facilitate rapid absorption of sublingually-administered medications)
- **molecular size** (e.g. drugs with large molecular weights (i.e. >1000 Da) are not as easily absorbed by passive diffusion as drugs with smaller molecular weights)
- **pH and drug ionization**
  - drugs are usually weak acids (e.g. ASA) or weak bases (e.g. ketoconazole) and thus exist in ionized and non-ionized forms in the body
  - non-ionized (uncharged) forms cross cell membranes more readily by passive diffusion than ionized (charged) forms
  - the ratio of ionized to non-ionized forms is determined by body compartment pH and drug pKa (as per the Henderson-Hasselbalch equation)
- **total surface area for absorption** (e.g. small intestinal villi have a large surface area and are the primary site of absorption for most orally-administered drugs)
- **drug transporters** (e.g. P-glycoprotein (P-gp), Organic anion transporting polypeptides (OATPs))

Bioavailability (F)
- **definition**: proportion of dose that reaches systemic circulation in an unchanged state that is available to access the site of action
- lower F usually reflects limited drug absorption or significant presystemic clearance (e.g. first-pass effect, substrate for drug transporters)
- IV dose has 100% bioavailability (F=1)

First-Pass Effect
- **definition**: metabolism (i.e. biotransformation) of the drug prior to reaching systemic circulation, resulting in reduced F
- can occur with PO administration of a drug: GI tract (absorption with possible metabolism) → portal vein to liver (possible first-pass metabolism) → systemic circulation
- with rectal administration, approximately 50% of drug absorbed goes through the portal system

Drug Transporters
- there are many drug transporters that can affect the uptake or efflux of drugs from cells and organelles, and affect drug absorption, distribution, and excretion
- P-gp is a transport protein of clinical relevance as it is found in a wide variety of body tissues (including the small intestinal epithelium, proximal tubule, bile canaliculi, and BBB) where it acts as a multidrug efflux pump and provides a "natural defence mechanism" against drugs and xenobiotics
- P-gp opposes the absorption of and enhances the elimination of many P-gp substrates (e.g. digoxin, etoposide, paclitaxel, tacrolimus, cyclosporine, apixaban)
- some drugs (e.g. most macrolide antibiotics) inhibit P-gp, leading to increased serum concentrations of P-gp substrates; P-gp inducers (e.g. rifampin, St. John's wort) increase efflux activity, leading to decreased serum concentrations of P-gp substrates
- some tumours overexpress P-gp, leading to multidrug resistance to chemotherapeutic agents
- other members of the ATP Binding Cassette (ABC) superfamily and the Solute Carrier (SLC) superfamily of drug transporters also affect drug absorption; members of the SLC superfamily generally function as uptake drug transporters

Distribution

- **definition**: movement of drugs between different body compartments, including their sites of action
- major body fluid compartments include plasma, interstitial fluid, intracellular fluid, and transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments include fat, muscle, and brain

Factors Affecting the Rate and Extent of Drug Distribution
- physical and chemical properties of the drug (e.g. $P_{o/w}$, pKa, and molecular weight)
- pH of fluid
- binding to plasma proteins
- binding within compartments (i.e. depots such as heart muscle, bone, fat tissue)
- regional blood flow
- drug transporters

Plasma Protein Binding
- some drug molecules bind to plasma proteins in the blood and exist in an equilibrium of two forms:
  1. bound to plasma protein: acidic drugs bind to albumin, basic drugs bind to α1-acid glycoprotein
  2. free (unbound): can leave the circulation to distribute into tissues and exert an effect, subject to metabolism and elimination
- bound fraction is determined by drug concentration, binding affinity, and plasma protein concentration (number of binding sites)
- reduced number of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in increased concentration of free drug, which is often cleared with no harmful effects, although toxicity is possible

Volume of Distribution
- V_d: the apparent volume of fluid into which a drug distributes
- a calculated value (V_d) = amount of drug in body (i.e. dose administered) ÷ initial plasma drug concentration
- a theoretical value that does not correspond to an actual physiologic volume; V_d can greatly exceed TBW
  - Total Body Water (TBW) represents the maximal anatomical fluid volume thought to be accessible to a drug (~40 L for average adult)
- small V_d (e.g. <0.04 L/kg) generally corresponds to a drug that distributes in plasma and/or binds plasma proteins to a high degree
- large V_d corresponds to a drug that preferentially distributes into tissues (e.g. fat, muscle, etc.); since most of the drug is not located in blood, the measured drug concentration in blood is low; thus, when dividing the dose by the blood/plasma drug concentration, it "appears" to distribute in a large volume
- V_d of drugs that are highly bound to plasma proteins can be altered by liver and kidney disease due to changes in plasma protein binding

- V_d of drugs changes with age
- V_d of drugs may change in the geriatric population based on the drug $P_{o/w}$; as there is often a reduction in total body water and total muscle mass, but an increase in total body fat in older adults, resulting in an increase in the V_d of hydrophobic drugs

Depot
- a body compartment in which drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam, THC)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate dosed q3 mo; depot risperidone dosed q2 wk)

Barriers (Relative)
- anatomical body structures that limit or prevent diffusion of drug molecules, such as the placenta or BBB (a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- physiological barriers such as drug transporters (e.g. P-gp), often serve as a natural defence mechanism against drugs and xenobiotics
- need to consider dosing route and/or drug interactions for drug penetration across these barriers
- barriers are important in determining sites of action and side effect profiles of drugs (e.g. risk of CNS depression if drug crosses BBB, risk of harm to a fetus if drug crosses placenta)

Metabolism (Biotransformation)

- **definition:** chemical transformation of a drug in vivo
- sites of biotransformation include the liver (main), GI tract, lung, plasma, kidney, and most other tissues
- as a result of the process of biotransformation:
  - a prodrug (i.e. inactive drug) may be activated (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be changed to another active metabolite (e.g. diazepam to oxazepam and others)
  - a drug may be changed to a toxic metabolite (e.g. acetaminophen to NAPQI)
  - a drug may be inactivated, as with most drugs (e.g. acetaminophen to acetaminophen glucuronide)

Drug Metabolizing Pathways
- phase I reactions
  - oxidation, reduction, or hydrolysis reactions that introduce or unmask polar groups on a parent compound to slightly increase water solubility (e.g. hydroxylation, demethylation)
  - the change in $P_{b/w}$ is typically minimal compared to phase II, and often phase I places a polar "handle" on a hydrophobic drug to permit conjugation in phase II
  - often mediated by cytochrome P450 (CYP) enzymes found in the endoplasmic reticulum (primarily in hepatocytes, but in lots of other tissues)
  - products of the reaction can be excreted or undergo further phase II reactions
- phase II (conjugation) reactions
  - conjugation with large endogenous substrates that are often polar (e.g. glucuronic acid, glutathione, sulphate, acetyl groups, methyl groups, or amino acids)
  - often substantially increases water solubility and renal elimination
  - can result in biologically active metabolites (e.g. morphine glucuronide)
  - can occur independently of phase I reactions (e.g. morphine to morphine glucuronides)

Examples of CYP Substrates, Inhibitors, and Inducers
drug-interactions.medicine.iu.edu/MainTable.aspx

Factors Affecting Drug Biotransformation
- **genetic polymorphisms** of metabolizing enzymes
  - for some enzymes, individual genotypes may alter the rate of drug metabolism (e.g. poor, intermediate, extensive, or ultra-rapid metabolizers, with extensive being considered the "normal" or average condition)
  - may lead to toxicity (e.g. if poor metabolizer) or ineffectiveness (e.g. if ultra-rapid metabolizer) of a drug at a normal dose
  - tamoxifen, tramadol, and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas hypermorphic alleles impart "ultra-rapid metabolizer" phenotype)
  - warfarin is metabolized by CYP2C9 (loss-of-function alleles lead to higher drug concentrations, greater effect and lower dose requirements)
- **enzyme inhibition** may result from other chemical exposures including drugs and foods
  - CYP inhibition leads to an increased concentration and bioavailability of the substrate drug (e.g. erythromycin (CYP3A4 inhibitor) can predispose patients to simvastatin (CYP3A4 substrate) toxicity)
  - grapefruit juice is a potent inhibitor of intestinal CYP3A4, resulting in markedly reduced first-pass metabolism and numerous drug interactions (e.g. saquinavir AUC increased 3-fold, simvastatin AUC increased 17-fold)

- **enzyme induction** may be due to the same or other medications
  - for example, certain medications enhance gene transcription to increase the activity of metabolizing enzymes
  - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of oral contraceptive pills) by inducing the CYP system
- **liver dysfunction** (e.g. hepatitis, alcoholic liver disease, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but it is not always clinically significant due to the liver's reserve capacity
- **renal disease** often results in decreased drug metabolism
- **extremes of age** (neonates or elderly) have reduced biotransformation capacity, but toddlers often have increased capacity, and doses should be adjusted accordingly
- **nutrition** may be involved, as insufficient protein and fatty acid intake decreases biotransformation, and vitamin/mineral deficiencies may also impact metabolizing enzymes
- **alcohol** has varying effects; while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1, increasing the risk of hepatocellular damage from acetaminophen by increasing the production of the toxic metabolite (NAPQI)
- **smoking** can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. theophylline, clozapine)

Excretion

- **definition**: removal of a drug from the body

Routes of Drug Excretion

- **kidney** (main organ of excretion)
  - renal drug clearance = (glomerular filtration + tubular secretion) – (tubular reabsorption)
  - renal function (assessed using serum creatinine) decreases with age (7.5 mL/min per decade) and is affected by many disease states (e.g. diabetes)
  - processes affecting renal excretion:
    1. glomerular filtration
       - a passive process, thus only the free drug fraction can be eliminated
       - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
    2. tubular secretion
       - a saturable transport process allowing both protein-bound and free drug fractions to be excreted
       - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, metformin)
       - drugs may block the secretion of other drugs if one or more share or inhibit the same drug transporter (e.g. probenecid can inhibit the excretion of penicillin via organic anion transporters)
    3. tubular reabsorption: some drugs can be actively or passively reabsorbed back into the systemic circulation, reducing their excretion
- **stool:** some drugs and metabolites are actively secreted into the bile or directly into the GI tract
  - enterohepatic recirculation occurs when drugs are reabsorbed from the intestine and returned to the liver to cycle between the intestine and liver, which can prolong the drug's duration in the body (e.g. some glucuronic acid conjugates that are excreted in bile may be hydrolyzed in the intestines by bacteria back to their original form and can be systemically reabsorbed)
- **lungs:** elimination of anesthetic gases and vapours by exhalation
- **other routes:** sweat, saliva, and breast milk are generally less significant routes, but saliva concentrations of some drugs parallel their plasma concentrations (e.g. rifampin) and drug excretion into breast milk is a concern for some drugs

Pharmacokinetic Considerations

- **definition**: the term "pharmacokinetics" is used to describe given aspects of drug disposition (i.e. the fate of drugs in the body) and encompasses absorption, distribution, metabolism, and excretion (ADME)
- absorption, distribution, and elimination can be graphically represented (e.g. a graph of concentration vs. time)

Time Course of Drug Action

- many kinetic parameters are measured after IV dosing because it avoids the complications of incomplete absorption, and distribution for most drugs is rapid
- when drug doses or concentrations are plotted vs. time, the dose or concentration plotted on the x-axis is often converted to a logarithmic scale (commonly $\log_{10}$) to allow for easier mathematical calculations
- the shape of the elimination phase of a concentration (or dose) or log-concentration (or log-dose) vs. time curve indicates whether the drug undergoes a first-order rate of elimination (visualized as a straight line on a log-dose or log concentration vs. time curve) or a zero-order rate of elimination (curvilinear on a log-dose or log-concentration vs. time curve)
- drugs such as warfarin can exhibit hysteresis (for a single drug concentration, there may be two different response levels)

Half-Life
- definition: time taken for the serum drug concentration to decrease by 50%; usually referred to as the elimination half-life
- applies only to drugs with first-order kinetics (i.e. most drugs), which require approximately four to five half-lives to reach steady-state with repeated dosing, or for complete drug elimination once dosing is stopped

Steady-State Drug Concentration
- drug concentration remains constant when the amount of drug entering the system is equivalent to the amount eliminated from the system
- determination of drug concentrations in therapeutic drug monitoring is of greatest utility when steady-state concentration has been reached
- special dosing situations
  - use a loading dose for drugs with a long half-life and/or when there is a clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin, some antibiotic settings)
  - use continuous infusion for drugs with a very short half-life and when there is a need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, unfractionated heparin, naloxone)

Clearance Rate
- quantitative measurement of the volume of body fluid from which a substance is removed per unit time
- Cl = rate of elimination of drug ÷ plasma drug concentration
- may be determined for a particular organ (e.g. liver or kidney), but if not specified, represents the total body clearance rate determined from the sum of individual clearance rates or by determining ke x Vd, where ke is the elimination rate constant equal to ln 2/half-life

Elimination Kinetics
- first-order kinetics (most common type)
  - constant proportion of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the Cl is less than would be predicted for a given concentration
  - shows linear relationship when plotted on a graph of concentration (log) vs. time (linear)
  - the concentration axis is converted to a log scale to allow for easier mathematical calculations
- non-linear or zero-order kinetics (less common, applies to a few drugs in the therapeutic range (e.g. alcohol, phenytoin, Aspirin®) and is more commonly associated with overdose)
  - constant amount of drug eliminated per unit time, regardless of concentration; the concept of half-life does not apply
  - saturation of various ADME processes creates non-linear kinetics, with first-order exhibited at lower concentrations and zero-order exhibited at higher concentrations after saturation
  - the complexity of dosing drugs with non-linear kinetics has resulted in the creation of drug-specific nomograms to aid clinicians in dosing, with these drugs often being the target of TDM (e.g. phenytoin, theophylline)

Loading and Maintenance Doses
- loading doses are used when an immediate effect is needed, with parenteral administration being the most common way of giving a large dose to "fill up" the volume of distribution for drugs that distribute extensively outside the vascular compartment
- maintenance doses can be given after a loading dose, but are most commonly initiated without a loading dose
  - steady-state levels are achieved after approximately four to five half-lives
  - can be given as either a continuous infusion (rare) or more commonly as intermittent oral doses

Pharmacodynamics
- study of "what the drug does to the body"
- **definition:** study of the effects of the drug on the body

Dose-Response Relationship
- graded dose-response relationship: relates dose to intensity of effect

Efficacy
- the relative ability of a drug to produce a maximal (biological/biochemical) response
- measured by E_{max} (the maximal response that a drug can elicit)

Potency

- measured by EC_{50} (the concentration of a drug needed to produce 50% of E_{max}); ED_{50} if dose is used (derived from graded dose-response curves)
- a drug that reaches its EC_{50} at a lower concentration is more potent (e.g. in Figure 1, drug A is more potent than drug B)

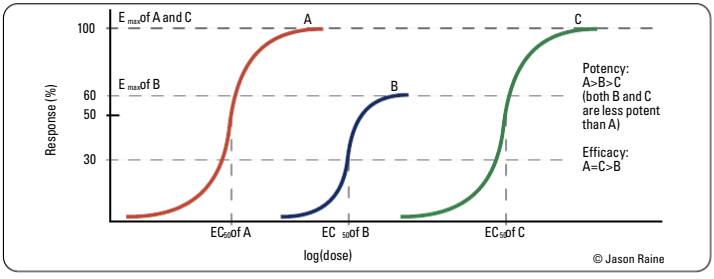


Figure 1. Log(dose)-response curve illustrating efficacy and potency

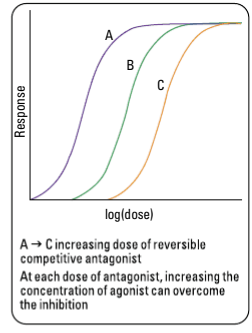

A
B
C
Response
log(dose)
A → C increasing dose of reversible competitive antagonist
At each dose of antagonist, increasing the concentration of agonist can overcome the inhibition

Figure 2. The log(dose)-response curve for reversible competitive antagonism

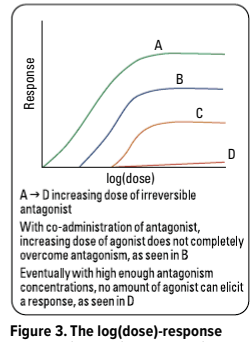

A
B
C
D
Response
log(dose)
A → D increasing dose of irreversible antagonist
With co-administration of antagonist, increasing dose of agonist does not completely overcome antagonism, as seen in B
Eventually with high enough antagonism concentrations, no amount of agonist can elicit a response, as seen in D

Figure 3. The log(dose)-response curve for irreversible antagonism

Effects of Drugs on Receptors

Agonists

- drugs that mimic the effects of the endogenous ligand and evoke a response when bound to the receptor
  - **affinity**: the ability and strength of the agonist to bind to the receptor (e.g. the β2-agonist salbutamol has greater affinity for β2-receptors than β1-receptors, thus it binds preferentially to β2-receptors)
  - **efficacy**: the ability to elicit a response via the receptor interaction (e.g. binding of salbutamol to β2-receptors results in smooth muscle relaxation)
    - drug efficacy is often determined under ideal conditions whereas drug effectiveness is a better measure of how the drug works in real-world situations
- full agonists: can elicit a maximal effect at a receptor (e.g. methadone or morphine on the μ opioid receptor system)
- partial agonists: can only elicit a partial effect, irrespective of the concentration at the receptor; also known as a ceiling effect (i.e. reduced efficacy compared to full agonists) (e.g. buprenorphine on the μ opioid receptor system)

Antagonists

- drugs that reduce the action of an agonist drug or of an endogenous ligand
- **chemical antagonism**: direct chemical interaction between agonist and antagonist prevents agonist-receptor binding (e.g. chelating agents for the removal of heavy metals, such as charcoal)
- **physiological/functional antagonism**: drugs that produce opposite physiological effects (e.g. insulin decreases blood glucose levels through its action at insulin receptors vs. glucagon raises blood glucose levels through its action at glucagon receptors)
- **pharmacological antagonism**: antagonist binds to the same site as the agonist or an alternative effector site and reduces the ability of the agonist to bind
  - **competitive antagonism**: antagonist binds directly to the active site on a given receptor, without activating it (i.e. zero efficacy) and prevents the agonist from binding to the active site
    - **reversible competitive antagonists**: bind non-covalently to the receptor, thus increasing concentrations of agonist may overcome the antagonist (e.g. naloxone is a competitive antagonist to morphine or heroin)
    - **irreversible competitive antagonists**: form a covalent bond with the receptor and cannot be displaced, thus irreversibly blocking other substrates from binding (e.g. phenoxybenzamine forms a covalent bond with adrenergic receptors preventing adrenaline and NE from binding)
  - **non-competitive antagonism**: antagonist (negative allosteric modulator) binds to an alternate site on the receptor which is distinct from the active site, producing allosteric effects that reduce the ability of the agonist to bind

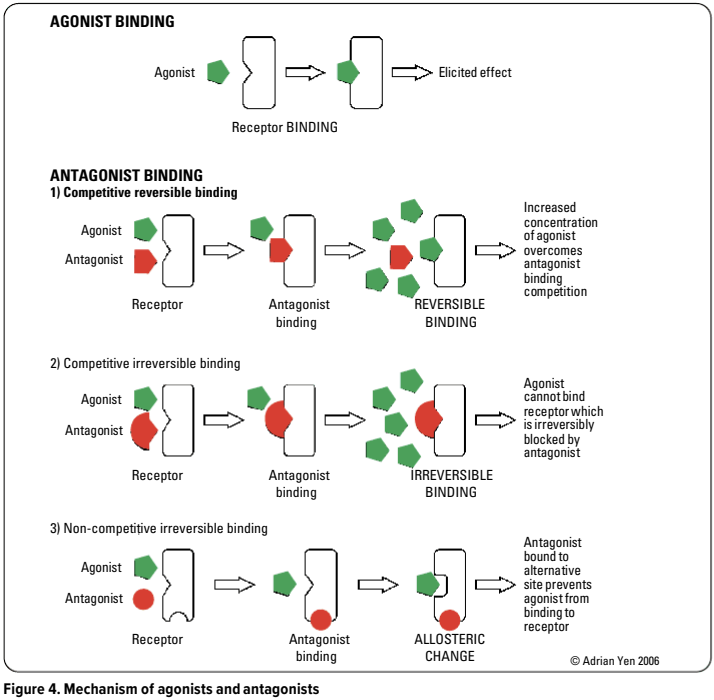
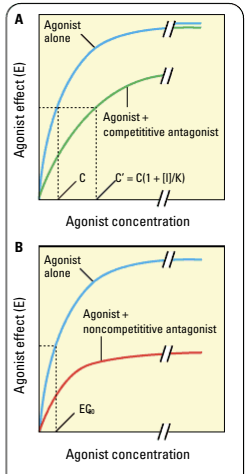


Figure 4. Mechanism of agonists and antagonists



Changes in agonist concentration effect curve produced by a reversible competitive agonist (**A**), and a non-competitive agonist (**B**). When a reversible competitive antagonist is present, a higher concentration of the drug (agonist) is required to create an effect. Therefore, the drug concentration C′ needed to create an effect in the presence of concentration [I] of a reversible competitive antagonist is shifted to the right. High agonist concentrations can overcome inhibition in the presence of a reversible competitive antagonist. This is not the case with an irreversible (or a non-competitive) antagonist, which reduces the maximal effect the agonist can achieve, although it may not change the EC_{50}

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Figure 5. Agonist concentration

Effectiveness and Safety

Effectiveness

- ED_{50} (effective dose): the dose of a drug needed to elicit a therapeutic effect in 50% of a test population (derived from quantal dose-response curves)

Safety

- LD_{50} (lethal dose): the dose of a drug needed to cause death in 50% of a test population of subjects (usually derived from animal or cell data)
- TD_{50} (toxic dose): the dose of a drug needed to cause a harmful effect in 50% of a test population of subjects (usually derived from animal or cell data)

Therapeutic Indices

Therapeutic Index: TD_{50}/ED_{50} (LD_{50}/ED_{50} in animals)

- a measure of relative drug safety often used when comparing drugs to examine the likelihood of a therapeutic dose to cause serious toxicity or death
- the larger the TI, the safer the drug
- common drugs with a narrow therapeutic window or low TI that sometimes require TDM include digoxin, theophylline, warfarin, lithium, and cyclosporine
- factors that can change the TI include presence of interacting drugs, changes in drug ADME, and patient characteristics (e.g. age, pregnancy, and organ impairment)

Certain Safety Factor: TD_1/ED_{99}

- a comparison of the dose that is effective in at least 99% of the population and toxic in less than 1% of the population
- regulatory agencies often like to see a certain safety factor or margin of safety above 100

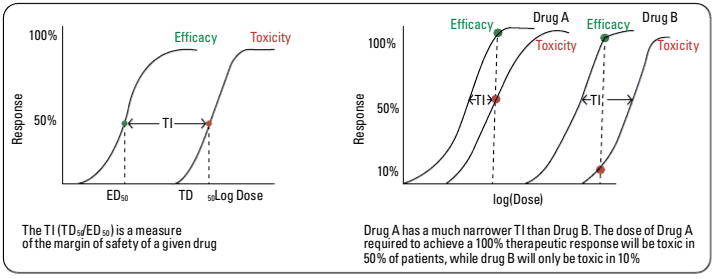

Figure 6. ED_{50}, TD_{50}, and the TI

Therapeutic Drug Monitoring

- **definition**: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance). Serum drug samples are usually taken when the drug has reached steady-state (i.e. after approximately 4-5 half-lives)
- TDM is often used for drugs that have low TIs, unpredictable dose-response relationships, significant consequences associated with therapeutic failure or toxicity, and/or wide interpatient PK variability
- nomograms are often used for low TI drugs, particularly in the setting of patients with complex clinical factors such as renal insufficiency, hepatic failure, dialysis, and hypoalbuminemia
- examples of drugs that sometimes require TDM include:
  - vancomycin
  - aminoglycosides (gentamicin, tobramycin)
  - digoxin
  - phenytoin and other anticonvulsants
  - warfarin
  - lithium

Adverse Drug Reactions

- **definition**: ADEs are events that occur while a patient is on a drug at either appropriate or inappropriate dosage. A causal relationship is not required
- **definition**: ADRs are reactions to drugs that occur when a drug is used for the appropriate indication at normal therapeutic doses

Table 2. Characteristics of Type A-E Adverse Drug Reactions

Classification	Definition	Characteristics
A (Augmented)	Dose-related	Predictable extension of drug's pharmacologic effect (e.g. β-blockers causing bradycardia) >80% of all ADRs
B (Bizarre)	Not dose-related	Reactions unrelated to the known pharmacological actions of the drug, generally with a genetic basis E.g. drug hypersensitivity syndromes, immunologic reactions (e.g. penicillin hypersensitivity), and idiosyncratic reactions (e.g. malignant hyperthermia)
C (Chronic)	Dose- and time-related	Related to cumulative doses Effects are well-known and can be anticipated (e.g. atypical femoral fracture from bisphosphonates, retinal toxicity from hydroxychloroquine)
D (Delayed)	Time-related	Occurs some time after use of drug (e.g. cardiovascular toxicity following doxorubicin therapy) May also be dose-related
E (End of use)	Withdrawal	Occurs after cessation of drug use (e.g. opioid withdrawal resulting from opioid dependence)

Tips to Reduce Drug-Related Adverse Events in the Elderly

- Be mindful of longstanding medications that have never been adjusted for patient age, renal function, or hepatic function
- Consider whether medications initiated during hospital admission are needed long-term (and whether the discharge dose is appropriate for maintenance)
- Avoid polypharmacy by decreasing the dose of or discontinuing medications that are causing side effects or are no longer indicated (i.e. deprescribing)
- Verify adherence to medications before automatically increasing the dose of subtherapeutic treatment
- When prescribing medications, preferentially use those with a high TI
- Review the patient's problem list and reconcile current medications to avoid duplication or inappropriate dosing/frequency

Antibiotic Allergies - What is the Risk of Cross-Reactivity?

- In clinical practice, cross-reactivity between drugs presents a problem for both patients and physicians
- In the case of penicillin allergy, cross-reactivity to cephalosporins is less than 2%. However, in patients who have a history of true anaphylactic reaction, cross-reactivity is closer to 40% depending on the side chain
- Cross-reactivity between penicillins and carbapenems is <1%
- The term "sulfa allergy" is often misused and has no formal definition. Current evidence suggests cross-reactivity between sulfonamide antibiotics (e.g. sulfamethoxazole-trimethoprim) and non-antibiotic sulfonamides, including loop diuretics (e.g. furosemide), thiazide diuretics (e.g. hydrochlorothiazide), protease inhibitors containing an arylamine group (e.g. darunavir), carbonic anhydrase inhibitors (e.g. acetazolamide), and sulfonylureas (e.g. glipizide)

Approach to Suspected Adverse Drug Reactions

- history and physical exam: signs and symptoms of reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, de-challenge (response when drug is removed), and re-challenge (response when drug is given again, if applicable)
  - medication history should include prescription, non-prescription and over-the-counter, natural health products/samples, supplements, creams, ear/eye drops, inhalers, and nasal sprays
  - dosage, frequency, route of administration, and duration of use should be recorded for each
- differentiate between drug therapy vs. disease pathophysiology
- treatment of serious adverse drug reactions: stop the drug, supportive care, and symptomatic relief. Specific interventions (e.g. steroids, immunosuppressants) used for some ADRs
- resources: check recent literature, Health Canada, and FDA; contact the pharmaceutical company; call Poison Control (1-800-268-9017) if overdose or poisoning suspected; check with MotherToBaby (https://mothertobaby.org/) in cases involving pregnant or breastfeeding women
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity
  - Canadian Adverse Drug Reaction Monitoring Program available for online reporting
    - https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug/health-care-providers.html

Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements due to age, genetics, disease states, drug interactions, diet, environmental factors, etc.
- possible causes of individual variability in drug response include problems with:
  - intake: medication adherence
  - absorption: vomiting, diarrhea, or steatorrhea; first-pass effect increased due to enzyme induction or decreased due to enzyme inhibition or liver disease
  - pharmacokinetic or pharmacodynamic drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, and fluoroquinolones in the GI lumen, impairing absorption)
  - distribution: very high or low percentage body fat, intact or disrupted BBB, patient is elderly or a neonate, or has liver dysfunction
  - biotransformation and elimination: certain genetic polymorphisms or enzyme deficiencies related to drug metabolism (e.g. acetylcholinesterase deficiency, CYP polymorphism), kidney or liver dysfunction
  - PD: genetic variability in drug response (e.g. immune-mediated reactions), diseases that affect drug PD, drug tolerance or cross-tolerance

Drug Interactions

- concomitant medications (including natural health products, e.g. St. John's wort) or foods (e.g. grapefruit juice): one drug alters the effect of one or more other drugs by changing PK and/or PD
- PK interactions involve changes in drug concentration when a new drug is added
  - absorption: alterations in gastrointestinal pH, gastric mucosa and/or emptying, intestinal motility, and/or transporter function
  - distribution: alterations in blood flow, plasma protein binding, anatomical and/or functional barriers (e.g. drug transporters)
  - metabolism: alterations in drug metabolism
  - excretion: alterations in renal or hepatic excretion
- PD interactions are due to two or more drugs that exert similar effects (additive or synergistic) or opposing effects (antagonistic)

Examples of Clinically Relevant Drug Interactions

Interaction	Potential Effect	Mechanism of Interaction
Warfarinplus ciprofloxacin, clarithromycin, erythromycin, metronidazole, or trimethoprim-sulfamethoxazole	Increased effect of warfarin	Multiple proposed PK and PD mechanisms (including antibiotic interference with enteric flora-mediated Vitamin K2 production and alterations in drug metabolism)
Warfarinplus acetaminophen	Note that this is not with typical use, but with more chronic and higher dose use	Acetaminophen (NAPQI) further increases INR	PD (reduction of Vitamin K-dependent clotting factors by NAPQI)
Oral contraceptive pills plus rifampin	Decreased effectiveness of oral contraception	PK (rifamycin induces CYP3A4, which increases hormone metabolism)
Sildenafilplus nitrates	Hypotension	PD (both PDE5 inhibitors and nitrates potentiate cGMP production)
SSRIsplus St. John's wort	Serotonin syndrome	PD (concomitant use of serotonergic medications)
SSRIsplus selegiline or non-selective MAOI	Serotonin syndrome	PD (all decrease metabolism of serotonin, so excess serotonin in synaptic cleft)
Some**HMG-CoA reductase inhibitors**plus niacin, gemfibrozil, erythromycin or itraconazole	Possible rhabdomyolysis	PK (various mechanisms based on drugs listed; CYP3A or OATP1B1, e.g. clarithromycin inhibits)
Sulfamethoxazole-trimethoprimand ACEIs/ARBs, or spironolactone	Increased risk of hyperkalemia	PD (reduced renal potassium excretion in the presence of trimethoprim resulting from decreased sodium reabsorption as a result of inhibition of sodium channels in the distal tubule)

Autonomic Pharmacology

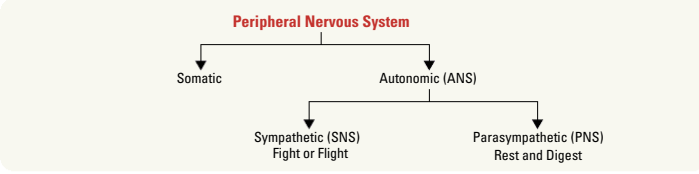

Figure 7. Subdivisions of the peripheral nervous system

- most organs are innervated by both sympathetic and parasympathetic nerves, which have opposing effects (see Neurology, N8)
- ACh and NE are the main neurotransmitters of the autonomic NS
- ACh binds to many cholinergic receptor subtypes, which include nicotinic and muscarinic receptors
- NE binds to adrenergic receptors, which principally include β1, β2, α1, and α2
- ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase
- acetylcholinesterase inhibitors (pyridostigmine, donepezil, galantamine, and rivastigmine) can be used to increase ACh levels in conditions such as myasthenia gravis or Alzheimer's disease
- NE action is terminated by reuptake at the presynaptic membrane, diffusion from the synaptic cleft, and degradation by monoamine oxidase (MAO) and COMT

Parasympathetic Nervous System

- blood vessels, sweat glands, the spleen capsule, and adrenal medulla do NOT have parasympathetic innervation
- parasympathetic pre-ganglionic fibres originate in the lower brainstem from cranial nerves III, VII, IX, and X, and in the sacral spinal cord at levels S2-S4. For this reason, it is sometimes referred to as the "craniosacral" nervous system. They connect with post-ganglionic fibres via nicotinic receptors in ganglionic cells located near or within the target organ (e.g. ciliary ganglion)
- post-ganglionic fibres connect with effector tissues via:
  - M1 muscarinic receptors located in the CNS
  - M2 muscarinic receptors located in smooth muscle, cardiac muscle, and glandular epithelium

Sympathetic Nervous System

- sympathetic preganglionic fibres originate in the spinal cord at spinal levels T1-L2/L3
- preganglionic fibres connect with postganglionic fibres via nicotinic receptors located in one of two groups of ganglia:
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. prevertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- post-ganglionic fibres connect with effector tissues via:
  - β1 receptors in cardiac tissue
  - β2 receptors in smooth muscle of bronchi and GI tract
  - α1 receptors in vascular smooth muscle
  - α2 receptors in vascular smooth muscle
  - M3 muscarinic receptors located in sweat glands

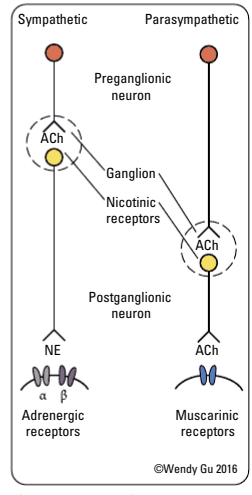

Figure 8. Autonomic nervous system efferent tracts

Table 3. Direct Effects of Autonomic Innervation on the Cardiorespiratory System

Organ	Sympathetic NS		Parasympathetic NS	
	Receptor	Action	Receptor	Action
Heart				
1. Sinoatrial	β1	Increased HR	M	Decreased conduction
2. Atrioventricular node	β1	Increased conduction	M	Decreased conduction
3. Atria	β1	Increased contractility	M	Decreased conduction
4. Ventricles	β1	Increased contractility	M	Decreased HR
Blood Vessels				
1. Skin, splanchnic	α1, β2	Constriction	M	Dilatation
2. Skeletal muscle	α	Constriction	M	Dilatation
3. Coronary	β2 (large muscles)	Dilatation	M	Dilatation
	α1, β2	Constriction	M	Dilatation
	β2	Dilatation	M	Dilatation
Lungs				
1. Bronchiolar smooth muscle	β2	Relaxation	M	Constriction
2. Bronchiolar glands	α1, β2	No stimulation	M	Stimulation

Opioid Therapy and Chronic Non-Cancer Pain

General Management Principles

- when first considering therapy for patients with chronic non-cancer pain, optimize non-opioid pharmacotherapy and non-pharmacologic therapy rather than starting a trial of opioids (strong recommendation)
- general approaches to opioid use include avoiding high doses, and when possible, a slow, collaborative approach when tapering
- for patients with chronic non-cancer pain beginning opioid therapy, restrict the prescribed dose to <90 MME/day, and ideally <50 MME/day, especially at starting dose
  - for patients with chronic non-cancer pain who are currently using 90 MME/day or more, encourage a slow, collaborative taper of opioids to the lowest effective dose, potentially discontinuing
- for patients with chronic non-cancer pain who are using opioids and experiencing serious challenges in tapering, a formal multidisciplinary program is suggested
- please refer to national opioid guidelines for a comprehensive approach to opioid use (https://www.cmaj.ca/content/189/18/E659#sec-11)

Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs. Increased Pain at Taper Completion?
Pain Med 2019;20:2179-2197
Purpose: Support or refute the hypothesis that opioid tapering in chronic pain patients (CPPs) improves pain or maintains the same pain level by taper completion but does not increase pain levels.
Methods: Structured systematic review searching relevant subject headings. 20 studies met inclusion/exclusion criteria and were of type III/IV level evidence. Characteristics were abstracted for numerical analysis.
Results: Total of 2109 CPPs tapered in all studies combined. 8% of the studies showed that by taper completion, pain had improved. In 15% of the studies, pain remained the same.
Conclusions: There is consistent type 3 and 4 evidence that opioid tapering in CPPs reduces or maintains the same pain levels. Studies were marginal in quality and further controlled studies needed.

Common Drug Endings

Table 4. Common Drug Endings

Ending	Category	Example
-afil	PDE-5 inhibitor	sildenafil
-ane	Inhaled general anesthetic	halothane
-azepam	Benzodiazepine	lorazepam
-azole*	Antifungal	ketoconazole
-caine	Local anesthetic	lidocaine
-mab	Monoclonal antibody	adalimumab
-nib	Small molecular inhibitor	imatinib
-olol	β-blocker	propranolol
-prazole	Proton pump inhibitor	omeprazole
-pril	ACE inhibitor	captopril
-sartan	ARB	candesartan
-statin	HMG-CoA inhibitor	atorvastatin
-terol	β2 agonist	albuterol
-tidine	H2 antagonist	cimetidine
-tropin	Pituitary hormone	somatotropin
-vir	Antiviral	acyclovir
-zosin	α1 antagonist	prazosin

Note: This table provides the most common drug endings for which there are only a few exceptions (e.g. methimazole, an antithyroid; stanozolol is an anabolic steroid) and is not exhaustive
*Unless ending is -prazole

Dangerous Abbreviations, Symbols, and Dose Designations

- the abbreviations, symbols, and dose designations in *Table 5* should never be used when communicating medication information as they are frequently misinterpreted and involved in harmful medication error

Table 5. Dangerous Abbreviations, Symbols, and Dose Designations

Abbreviation/Symbol/Dose Designation	Intended Meaning	Problem	Correction
U	unit	Mistaken for "0" (zero), "4" (four), or cc	Use "unit"
IU	international unit	Mistaken for "IV" (intravenous) or "10" (ten)	Use "unit"
Abbreviations for drug names		Misinterpreted because of similar abbreviations for multiple drugs; e.g., MS, MSO_4 (morphine sulphate), $MgSO_4$ (magnesium sulphate) may be confused for one another	Do not abbreviate drug names
QD QOD	Every day Every other day	QD and QOD have been mistaken for each other, or as 'qid'. The Q has also been misinterpreted as "2" (two)	Use "daily" and "every other day"
OD	Every day	Mistaken for "right eye" (OD = oculus dexter)	Use "daily"
OS, OD, OU	Left eye, right eye, both eyes	May be confused with one another	Use "left eye", "right eye" or "both eyes"
D/C	Discharge	Interpreted as "discontinue whatever medications follow" (typically discharge medications)	Use "discharge"
cc	cubic centimetre	Mistaken for "u" (units)	Use "mL" or "millilitre"
µg	microgram	Mistaken for "mg" (milligram) resulting in one thousand-fold overdose	Use "mcg"
@	at	Mistaken for "2" (two) or "5" (five)	Use "at"
> <	Greater than Less than	Mistaken for "7" (seven) or the letter "L" . Confused with each other	Use "greater than"/"more than" or "less than"/"lower than"
Trailing zero	X.0 mg	Decimal point is overlooked resulting in 10-fold dose error	Never use a zero by itself after a decimal point. Use "X mg"
Lack of leading zero	. X mg	Decimal point is overlooked resulting in 10-fold dose error	Always use a zero before a decimal point. Use "0.X mg"

Adapted from Institute for Safe Medication Practices Canada (ISMP)'s List of Error-Prone Abbreviations, Symbols, and Dose Designations 2006

For more information on medical pharmacology, please refer to our textbook product
Pharmacology You See

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D Dermatology

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Acronyms

β-hCG	β-human chorionic gonadotropin
ACEI	angiotensin-converting enzyme inhibitor
AGEP	acute generalized exanthematous pustulosis
AD	atopic dermatitis
AK	actinic keratoses
ASO	anti-streptolysin O
BCC	basal cell carcinoma
BCG	bacillus Calmette-Guerin
BSA	body surface area
BUN	blood urea nitrogen
CMV	cytomegalovirus
CNS	central nervous system
Cr	creatinine
CXR	chest x-ray
DIHS	drug-induced hypersensitivity syndrome
DLE	discoid lupus erythematosus
DM	diabetes mellitus
DRESS	drug reaction with eosinophilia and systemic symptoms
DVT	deep vein thrombosis
EM	erythema multiforme
Er:YAG	erbium-doped yttrium aluminum garnet
ESR	erythrocyte sedimentation rate
Fe	iron
FTA-ABS	fluorescent treponemal antibody-absorption
GAS	group A β-hemolytic Streptococcus
GVHD	graft-versus-host disease
HHV	human herpes virus
HLA	human leukocyte antigen
HPA	hypothalamic-pituitary-adrenal
HPV	human papillomavirus
HRT	hormone replacement therapy
HSV	herpes simplex virus
HZV	herpes zoster virus
IBD	inflammatory bowel disease
IFN	interferon
IVIg	intravenous immunoglobulin
MAOI	monoamine oxidase inhibitor
MM	malignant melanoma
NB-UVB	narrow band ultraviolet B
Nd:YAG	neodymium-doped yttrium aluminum garnet
NMN	nevomelanocytic nevus
NMSC	nonmelanoma skin cancers
OCP	oral contraceptive pill
OTC	over-the-counter
PABA	para-aminobenzoic acid
PASI	psoriasis area and severity index
PDE-4	phosphodiesterase-4
PPD	purified protein derivative
PUVA	psoralens and UVA
RA	rheumatoid arthritis
SCC	squamous cell carcinoma
SJS	Stevens-Johnson syndrome
SPF	sun protection factor
SSRI	selective serotonin reuptake inhibitor
SSSS	staphylococcal scalded skin syndrome
STI	sexually transmitted infection
TB	tuberculosis
TCS	topical corticosteroid
TEN	toxic epidermal necrolysis
TMP/SMX	trimethoprim-sulfamethoxazole
UC	ulcerative colitis
URTI	upper respiratory tract infection
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
UVC	ultraviolet C
UVR	ultraviolet radiation
VDRL	venereal disease research laboratory
VZV	varicella zoster virus

Introduction to Skin

Normal Processes of Skin and Subcutaneous Tissue

Embryonic Development of the Skin

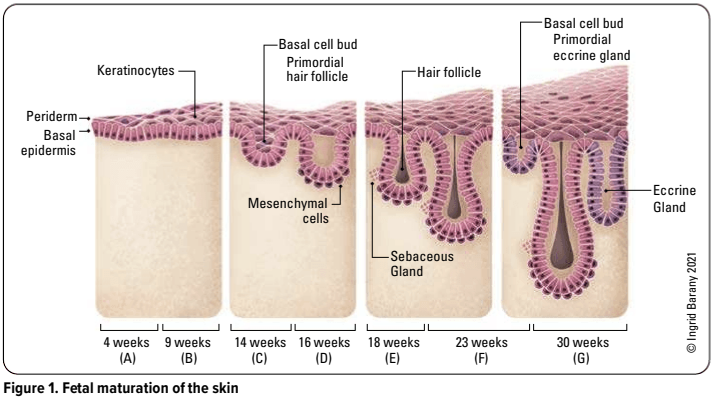

Figure 1. Fetal maturation of the skin
(A) 4 wk gestation: fetal skin has two distinct layers - the basal cell layer and outer layer (i.e. periderm). (B) 9 wk gestation: keratinization begins. (C) 14 wk gestation: stratification of epidermal layer; primordial hair follicle forms from the basal cell bud. (D) 16 wk gestation: local proliferation of mesenchymal cells associated with the epidermal buds as hair follicles develop and elongate. (E) 18 wk gestation: sebaceous gland develops; hair follicle elongates. (F) 23 wk gestation: continuous elongation of the hair follicle; primordial eccrine gland forms from the basal cell bud. (G) 30 wk gestation: continuous elongation and foiling coiling of the eccrine glands.
Modified from Facial Plastic Surgery Clinics of North America, 21(1), King A, Balaji S, Keswani SG, Biology and Function of Fetal and Pediatric Skin, 1-6, Copyright (2020), with permission from Elsevier

- **embryonic development and fetal maturation (see *Figure 1*)**
- **neonatal changes**
  - full-term infants have skin with all five layers, similar to adults
  - epidermal cells mature from columnar stratum basale to squamous keratinocytes of the stratum corneum
    - maturation occurs more rapidly in facial skin than trunk or limb skin
  - neonatal skin is coarser and develops into a more smooth texture homogeneously during the first 30 d of life
  - infants have smaller corneocytes and thinner stratum corneum until 2 y/o
  - from infancy to puberty, dermal thickness increases
- **repair, regeneration, and changes associated with stages of life**
  - regeneration relies on tissue-specific stem cells and restricted progenitor cells

- regenerative abilities decline with age as both cell types undergo:
  - a loss of self-renewing capacities
  - altered proliferative activity
  - functional decline
- with age, the skin becomes thinner and less able to withstand external stress because:
  - the epidermis attenuates with effacement of the rete ridges
  - keratinocytes lose proliferative abilities
  - the dermis loses volume
  - hyaluronic acid diminishes in the extracellular matrix of the dermis
- these changes lead to loss of skin and hair integrity, leading to conditions such as senile purpura and male pattern baldness (i.e. androgenic alopecia, see *D44*)
  - senile purpura (i.e. solar or actinic purpura): typically arise spontaneously; characterized by non-blanchable red-to-purple patches that resolve over 1-3 wk, leaving residual brown-yellow discolouration secondary to hemosiderin deposition
- the decline in regenerative ability can also be seen as postmenopausal hair changes (see *D46*)

Skin Anatomy

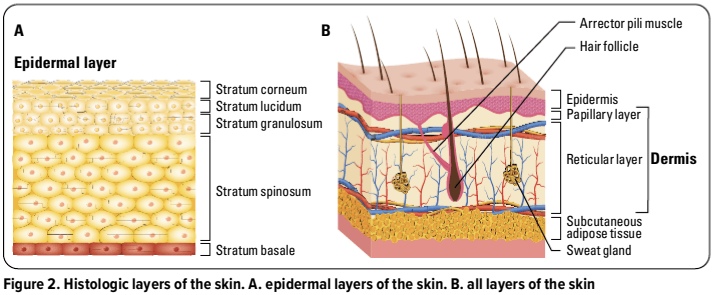

Figure 2. Histologic layers of the skin. A. epidermal layers of the skin. B. all layers of the skin

Layers of the Epidermis
"**C**alifornians **L**ike **G**oing **S**un **B**athing"
OR
"**C**anadians **L**ike **G**ood **S**ushi **B**oxes"

Skin

- divided anatomically into epidermis, dermis, and subcutaneous tissue
- **epidermis**
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale
  - cells progress from stratum basale to stratum corneum in about 4 wk
    - stratum basale (i.e. germinativum): mitotic figures that give rise to keratinocytes
    - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
    - stratum granulosum: flat cells containing basophilic granules
    - stratum lucidum: transparent layers of packed dead cells
    - stratum corneum: flat scales of the water-resistant protein keratin
  - cells of the epidermis:
    - keratinocytes: located in all layers of the epidermis except the stratum corneum; connected to each other by desmosomes
    - melanocytes: located in the stratum basale; keratinocyte:melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races; produce melanosomes containing melanin, which are transferred to keratinocytes
    - Langerhans cells: dendritic cells which are important for immune surveillance
    - Merkel cells: located in the stratum basale; involved in touch sensation
- **dermis**
  - comprised of connective tissue divided into two regions
    - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
    - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages
  - cells of dermis
    - fibroblasts: produce collagen, elastin, and ground substance
    - mast cells: release histamines which mediate type I hypersensitivity
  - other components of dermis include: blood vessels, nerves, pilosebaceous units, and sweat glands
- **subcutaneous tissue** (i.e. hypodermis)
  - consists primarily of adipose cells, larger calibre vessels, nerves, and fascia

Epidermal Appendages

- epidermal in origin, can extend into the dermis; includes hair, nails, and cutaneous glands
- pilosebaceous unit = hair + hair follicle + sebaceous gland + arrector pili muscle

Cutaneous Glands

- **sebaceous gland:** part of pilosebaceous unit; produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
  - sebum has some antifungal properties
  - these glands cover entire skin surface and are absent only in non-hair bearing areas (e.g. palms, soles, lips)
- **apocrine sweat gland:** apocrine duct empties into hair follicle above sebaceous gland
  - not part of pilosebaceous unit
  - found concentrated in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)
- **eccrine sweat gland:** not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds, and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface

Skin Function

- **protection**
  - due to continuous recycling and avascularity of epidermis, as well as normal skin flora
  - barrier to UV radiation (melanin), mechanical/chemical insults (sensory/mechanoreceptors), pathogens (immune cells), and dehydration (lipid rich barrier)
- **thermal regulation**
  - insulation to maintain body temperature in cool environments via peripheral vasoconstriction, hair, and subcutaneous adipose tissue
  - dissipation of heat in warm environments via increased activity of sweat glands and increased blood flow within dermal vascular networks
- **sensation**
  - touch, pain, and temperature sensation
- **metabolic function**
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

Morphology

Primary Lesions

Definition

- a de-novo initial lesion that has not been altered by trauma or manipulation, and has not regressed

Table 1. Types of Primary Morphological Lesions

Profile	<1 cm Diameter	≥1 cm Diameter
Flat Lesion	Macule (e.g. freckle)	Patch (e.g. vitiligo)
Raised Superficial Lesion	Papule (e.g. wart)	Plaque (e.g. psoriasis)
Deep Palpable (Dermal or Subcutaneous) Lesion	Nodule (e.g. dermatofibroma)	Tumour (e.g. lipoma)
Elevated Fluid-Filled Lesion	Vesicle (e.g. HSV)	Bulla (e.g. bullous pemphigoid)

Describe a Lesion with SCALDA

Size and Surface area
Colour (e.g. hyperpigmented, hypopigmented, erythematous)
Arrangement (e.g. solitary, linear, reticulated, grouped, herpetiform)
Lesion morphology
Distribution (e.g. dermatomal, intertriginous, symmetrical/asymmetrical, follicular)
Always check hair, nails, mucous membranes, and intertriginous areas

Secondary Lesions

Definition

- develop during the evolutionary process of skin disease, created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)

Types of Secondary Morphological Lesions

- **crust:** dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- **scale:** excess keratin (e.g. seborrheic dermatitis)
- **lichenification:** thickening of the skin and accentuation of normal skin markings (e.g. chronic AD)
- **fissure:** a linear slit-like cleavage of the skin
- **excoriation:** a scratch mark
- **erosion:** a disruption of the skin involving the epidermis alone; heals without scarring
- **ulcer:** a disruption of the skin that extends into the dermis or deeper; may heal with scarring
- **xerosis:** pathologic dryness of skin (xeroderma), conjunctiva (xerophthalmia), or mucous membranes (xerostomia)
- **atrophy:** histological decrease in size or number of cells or tissues, resulting in thinning or depression of the skin

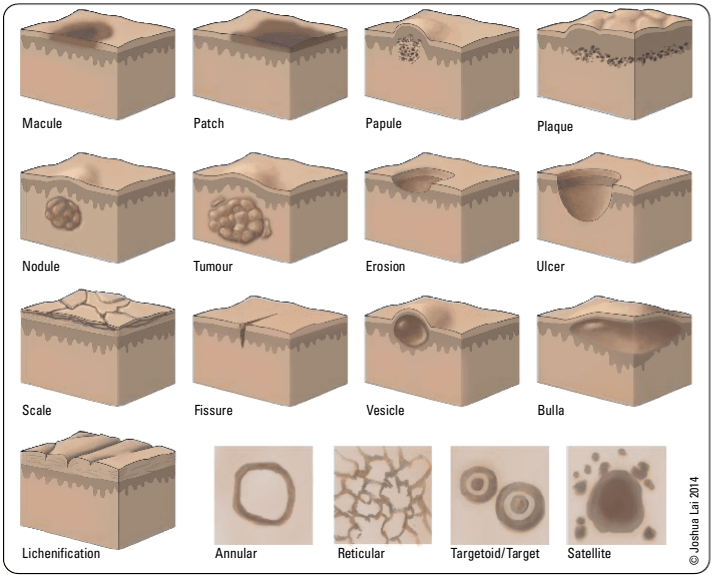

Figure 3. Examples of primary and secondary lesions

Other Morphological Terms

- **cyst**: an internally epithelial-lined structure containing semi-solid material or fluid
- pustule: an elevated lesion containing a collection of neutrophils (infectious or inflammatory in nature)
- **scar:** replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- **wheal:** a special form of papule or plaque that is transient (<24 h) and blanchable, often with a halo and central clearing, formed by edema in the dermis (e.g. urticaria)
- **comedone:** a special collection of sebum and keratin
  - open comedone (blackhead)
  - closed comedone (whitehead)
- **petechiae:** pinpoint extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, <3 mm in size
- **purpura:** larger than petechiae, 3 mm-1 cm in size
- **ecchymosis (i.e. bruise):** larger than purpura, >1 cm in size
- **telangiectasia:** dilated superficial blood vessels; blanchable, reticulated, and of small calibre, can be associated with benign or malignant entities

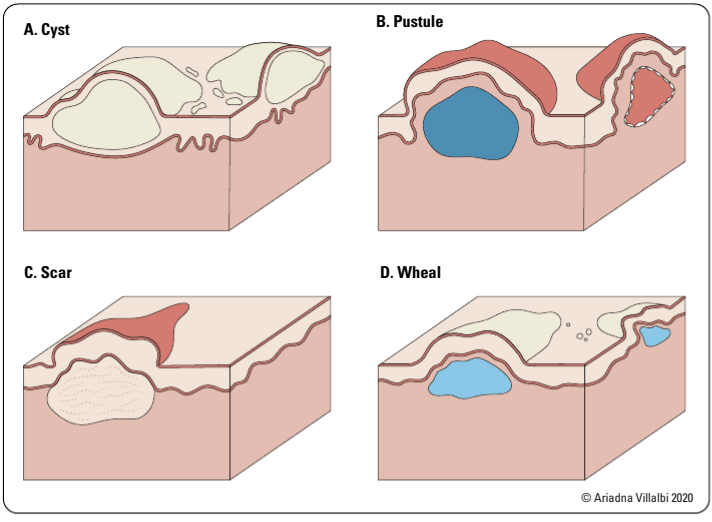

Figure 4. Examples of other morphological terms: cyst, pustule, scar, and wheal

Wolff K, Johnson R, Saavedra A, Fitzpatrick's Colour Atlas and Synopsis of Clinical Dermatology, Seventh Edition, copyright © 2020, Modified by Permission of McGraw-Hill Education

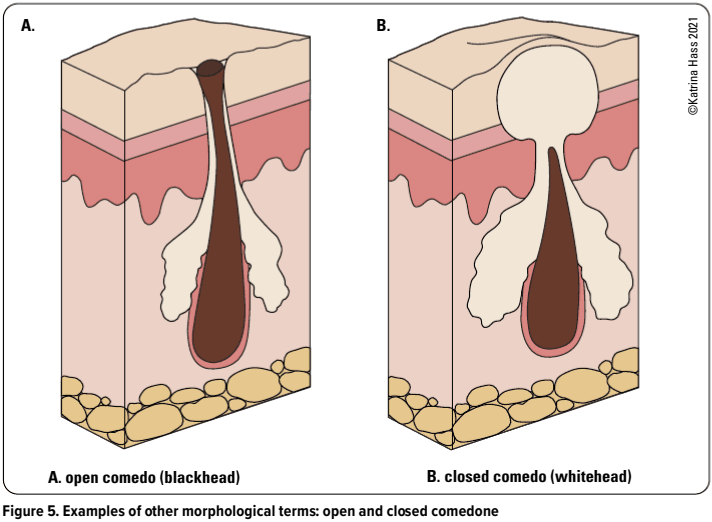

Figure 5. Examples of other morphological terms: open and closed comedone

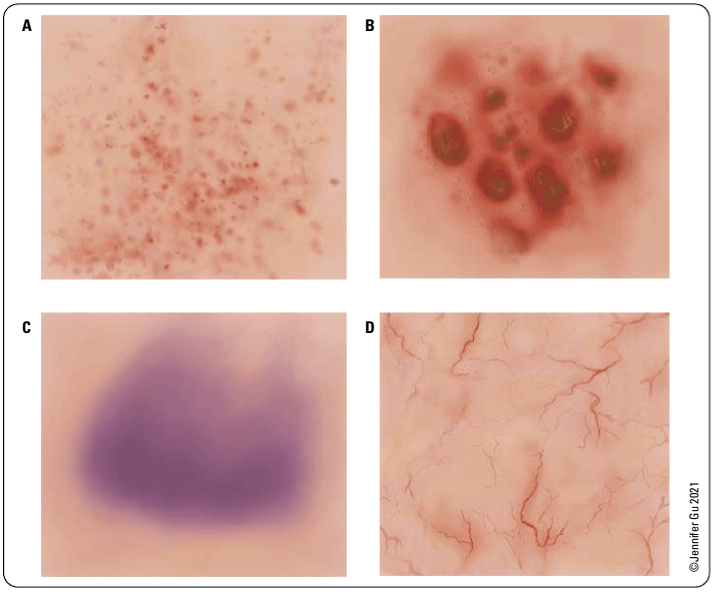

Figure 6. Examples of other morphological terms: A: petechiae, B: purpura, C: ecchymosis, and D: telangiectasia

Patterns and Distribution

Table 2. Patterns and Distribution of Morphological Lesions

Pattern or Distribution	Definition	Example
Acral	Relating to the hands and feet	Perniosis, secondary syphilis
Annular	Ring-shaped	Granuloma annulare
Follicular	Involving hair follicles	Folliculitis
Guttate	Lesions following a "drop-like" pattern	Guttate psoriasis
Koebner Phenomenon (i.e. isomorphic response)	Appearance of lesions at a site of skin injury	Lichen planus, psoriasis, vitiligo
Morbilliform	Literally means "measles-like," an eruption composed of macules and papules with truncal predominance	Morbilliform drug eruption
Reticular	Lesions following a "net-like" pattern	Livedo reticularis
Satellite	Small lesions scattered around the periphery of a larger lesion	Candida diaper dermatitis
Serpiginous	Lesions following a "snake-like" pattern	Cutaneous larva migrans
Target/Targetoid	Concentric ring lesions, like a bullseye	EM, urticaria, SJS/TEN

Other descriptive terms: discrete, clustered, linear, confluent, dermatitic, indurated (i.e. hard or firm)

Differential Diagnoses for Common Presentations

Table 3. Differential Diagnoses for Common Presentations

Lesion	Infectious	Inflammatory	Drug/Toxin	Miscellaneous
Brown Macule		Post-inflammatory hyperpigmentation	UV radiation, actinic/solar lentigo, freckle (i.e. ephelis)	Congenital: café-au-lait macule, congenital nevus, epidermal/junctional nevus Neoplasia: lentigo maligna, MM, pigmented BCC Other: melasma/chloasma (i.e. "mask of pregnancy")
Discrete Red Papule	Folliculitis Furuncle Scabies	Acne vulgaris Rosacea Psoriasis Urticaria	Bites/stings	Autoimmune: lichen planus Vascular: hemangioma, pyogenic granuloma Other: dermatofibroma, miliaria rubra

Table 3. Differential Diagnoses for Common Presentations

Lesion	Infectious	Inflammatory	Drug/Toxin	Miscellaneous
Red Scales	Pityriasis rosea Secondary syphilis Tinea	Dermatitis (atopic, contact, nummular, seborrheic) Discoid lupus Psoriasis	Gold	Autoimmune: lichen planus Neoplastic: mycosis fungoides
Vesicle	Cat scratch disease Impetigo Viral: HSV, HZV, VZV, Coxsackie virus Scabies	Acute contact dermatitis Dyshidrotic eczema		Other: dermatitis herpetiformis, porphyria cutanea tarda
Bulla	Bullous impetigo	Acute dermatitis EM, SLE, SJS/TEN	Fixed drug eruption SJS/TEN	Autoimmune: bullous pemphigoid, pemphigus vulgaris Other: dermatitis herpetiformis, porphyria cutanea tarda
Pustule	Candida Dermatophyte Impetigo Sepsis Varicella	Acne vulgaris Rosacea Dyshidrotic dermatitis Pustular folliculitis Pustular psoriasis Hidradenitis suppurativa	AGEP (usually secondary to drug reaction)	
Oral Ulcer	Aspergillosis CMV Coxsackie virus Cryptococcosis HSV/HZV HIV, TB, Syphilis	Allergic stomatitis EM Lichen planus Seronegative arthropathies, SLE Recurrent aphthous stomatitis Behçet's disease	Chemotherapy Radiation therapy SJS/TEN	Autoimmune: pemphigus vulgaris Congenital: XXY Hematologic: sickle cell disease Neoplasia: BCC, SCC
Skin Ulcer	Plague Syphilis TB Tularemia	RA, SLE, vasculitis UC, pyoderma gangrenosum		Autoimmune: necrobiosis lipoidica diabeticorum (e.g. DM) Congenital: XXY Hematologic: sickle cell disease Neoplasia: SCC Vascular: arterial, neurotrophic, pressure, venous, aphthous, leukoplakia, traumatic

Common Skin Lesions

Cysts

Table 4. Cysts

	Clinical Features	Pathophysiology	Epidemiology	Clinical Course	Management
Epidermal Cyst	Round, yellow/flesh-coloured, slow growing, mobile, firm, fluctuant, nodule, or tumour	Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris May be post-traumatic, rarely syndromic	Most common cutaneous cyst in youth-middle age	Central punctum may rupture (foul, cheesy odour, creamy colour) and produce inflammatory reaction Can increase in size and number over time	No treatment Elective excision
Pilar Cyst (i.e. Trichilemmal)	Multiple, hard, variable sized nodules under the scalp; lacks central punctum	Thick-walled cyst lined with stratified squamous epithelium and filled with dense keratin Idiopathic Post-trauma	2nd most common cutaneous cyst F>M, hereditary	Rupture causes pain and inflammation	No treatment Elective excision
Dermoid Cyst	Firm nodule most commonly found at lateral third of eyebrow or midline under nose	Rare, congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick-walled cyst filled with dense keratin	Rare	If nasal midline, risk of extension into CNS	No treatment Elective excision
Milium	1-2 mm superficial, white to yellow subepidermal papules occurring on eyelids, cheeks, and forehead	Small epidermoid cyst, primarily arising from pluripotential cells in epidermal or adnexal epithelium Can be secondary to blistering, ulceration, trauma, TCS, atrophy, or cosmetic procedures	Any age 40-50% of infants	In newborns, spontaneously resolves in first 4 wk of life	No treatment Incision and expression of contents Electrodessication Topical retinoid therapy

GANGLION CYST: See Plastic Surgery PL27

Fibrous Lesions

DERMATOFIBROMA

Clinical Features

- firm dermal papule or nodule, skin-coloured to red-brown
- majority are asymptomatic but may be pruritic and/or tender
- sites: legs > arms > trunk
- dimple sign (i.e. Fitzpatrick's sign): lateral compression causes dimpling of the lesion

Pathophysiology
- benign tumour due to fibroblast proliferation in the dermis

Etiology
- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibroma can be associated with SLE

Epidemiology
- adults, F>M

Differential Diagnosis
- dermatofibrosarcoma protuberans, melanoma

Investigations
- biopsy if diagnosis is uncertain

Management
- no treatment required
- excision if bothersome

SKIN TAGS

Clinical Features
- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

Pathophysiology
- benign outgrowth of skin

Epidemiology
- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

Differential Diagnosis
- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma, nevus lipomatosis superficialis

Management
- snip excision, electrodessication, cryosurgery

Hyperkeratotic Lesions

SEBORRHEIC KERATOSIS

Clinical Features
- i.e. 'wisdom spots,' 'age spots,' or 'barnacles of life'
- well-demarcated waxy papule/plaque with classic "stuck on" appearance
- occasionally pruritic
- over time lesions appear more warty, greasy, and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

Pathophysiology
- very common benign epithelial tumour due to proliferation of keratinocytes and melanocytes

Epidemiology
- unusual <30 y/o
- M>F
- autosomal dominant inheritance
- Leser-Trelat sign: sudden appearance of seborrheic keratosis that can be associated with malignancy, commonly gastric adenocarcinomas

Differential Diagnosis
- melanoma (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented AK

Investigations
- biopsy only if diagnosis uncertain

Management
- none required, for cosmetic purposes only
- cryotherapy, electrodessication, shave excision

ACTINIC KERATOSES (SOLAR KERATOSES)
- see *Pre-Malignant Skin Conditions, D39*

KERATOACANTHOMA
- see *Malignant Skin Tumours, D40*

CORNS (HELOMATA)

Clinical Features
- firm papule with a central, translucent, cone-shaped, hard keratin core
- painful with direct pressure
- sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

Pathophysiology
- localized hyperkeratosis induced by pressure on hands and feet

Epidemiology
- F>M, can be caused by chronic microtrauma

Differential Diagnosis
- calluses, plantar warts

Management
- relieve pressure with padding or alternate footwear, orthotics
- paring, topical salicylic acid, referral to podiatry

Corns vs. Warts vs. Calluses
- Corns have a whitish yellow central translucent keratinous core; painful with direct pressure; interruption of dermatoglyphics
- Warts bleed with paring and have a black speckled central appearance due to thrombosed capillaries; plantar warts destroy dermatoglyphics (epidermal ridges)
- Calluses have layers of yellowish keratin revealed with paring; there are no thrombosed capillaries or interruption of epidermal ridges

Keloids

Clinical Features
- firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
- extends beyond the margins of the original injury, and may continue to expand in size for yr with claw-like extensions
- can be pruritic and painful
- sites: earlobes, shoulders, sternum, scapular area, angle of mandible

Pathophysiology
- excessive deposition of randomly organized collagen fibres following trauma to skin

Epidemiology
- most common in Black patients, followed by those of Asian descent (predilection for darker skin)
- M=F, most commonly between ages 10-30

Management
- intralesional steroids
- silicone gel sheets

Keloids vs. Hypertrophic Scars

Keloids: extend beyond margins of original injury with claw-like extensions

Hypertrophic scars: confined to original margins of injury

DDx of Hyperpigmented Macules
- Purpura (e.g. solar, ASA, anticoagulants, steroids, hemosiderin stain)
- Post-inflammatory
- Melasma
- Melanoma
- Fixed drug eruption

Pigmented Lesions

CONGENITAL NEVOMELANOCYTIC NEVI (CNN)

Clinical Features
- i.e. congenital hairy nevi
- sharply demarcated pigmented papule or plaque with regular borders ± coarse hairs
- classified by size: small (<1.5 cm), medium (M1: 1.5-10 cm, M2: >10-20 cm), large (L1: >20-30 cm, L2: >30-40 cm), giant (G1: >40-60 cm, G2: >60 cm)
- may be surrounded by smaller satellite nevi

Pathophysiology
- nevomelanocytes in epidermis (clusters) and dermis (strands)

Epidemiology
- present at birth or develops in early infancy to childhood
- malignant transformation is rare (1-5%) and more correlated with size of the lesion
- neurocutaneous melanosis can occur in giant CNN (melanocytes in the CNS)

Management
- take a baseline photo and observe lesion for change in shape, colour, or size out of proportion with growth
- surgical excision if suspicious, due to increased risk of melanoma
- MRI if suspicious for neurological involvement

Other Nevi
- Halo nevus: often appears as a typical nevus surrounded by a ring of depigmentation; common in children; uncommonly associated with vitiligo; no treatment required unless irregular colour or borders
- Blue nevus: round to oval macule/papule with homogenous blue to blue-black colour; often appears in childhood and late adolescence; no treatment required unless atypical features are noted

Other Nevi
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Blue nevus: round to oval macule/papule with homogenous blue to blue-black colour; often appears in childhood and late adolescence; no treatment required unless atypical features are noted

OTHER CONGENITAL PIGMENTED LESIONS

Table 5. Comparison of Other Congenital Pigmented Lesions

	Clinical Features	Pathophysiology	Epidemiology	Differential Diagnosis	Clinical Course and Management
Café-au-lait Macule	Flat light-brown lesions with smooth or jagged borders	Areas of increased melanogenesis	Six or more is suggestive of neurofibromatosis type I Also associated with McCune-Albright syndrome	Flat congenital melanocytic nevus, speckled lentiginous nevus	Enlarge in proportion to the child No effective treatment
Speckled Lentiginous Nevus (i.e. nevus spilus)	Brown pigmented macular background (café-au-lait macule-like) with dark macular or papular speckles	Increased melanocyte concentration	Risk of melanoma similar to that of a CNN of the same size	Café-au-lait macule, agminated lentigines, Becker's nevus	Usually the light macular background is present at birth and speckles develop over time Management is similar to that of CNNs
Dermal Melanocytosis (historically known as Mongolian Spot)	Congenital grey-blue solitary or grouped macules commonly on lumbosacral area	Ectopic melanocytes in dermis	99% occurs in Asian and Indigenous infants	Ecchymosis	Usually fades in early childhood but may persist into adulthood
Xeroderma Pigmentosum	Extreme sensitivity to UV light, redness and blistering, xerosis, and changes in skin colour Typically affects the eyes and sun-exposed areas; may affect nervous system	Involves mutations in genes responsible for DNA repair (e.g. nucleotide excision repair genes)	More common in Japan, North Africa, and the Middle East	Freckles, Rothmund-Thomson syndrome, and porphyrin disease	Prevention by avoiding sun exposure (damage is irreversible) Reduce incidence of cancer using anticancer drugs (e.g. isotretinoin, fluorouracil) in adults only

ACQUIRED NEVOMELANOCYTIC NEVI (NMN)

Clinical Features
- common mole: well circumscribed, round, uniformly pigmented macules/papules <1.5 cm
- average number of moles per person: 18-40
- three stages of evolution: junctional NMN, compound NMN, and dermal NMN

Table 6. Evolution of Acquired Nevomelanocytic Nevi

Type	Age of Onset	Clinical Feature	Histology
Junctional	Childhood Majority progress to compound nevus	Flat, regularly bordered, uniformly tan-dark brown, sharply demarcated macule	Melanocytes at dermal-epidermal junction above basement membrane
Compound	Any age	Domed, regularly bordered, smooth, round, tan-dark brown papule Face, trunk, extremities, scalp NOT found on palms or soles	Melanocytes at dermal-epidermal junction; migration into dermis
Dermal	Adults	Soft, dome-shaped, skin-coloured to tan/brown papules or nodules Sites: face, neck	Melanocytes exclusively in dermis

Management
- new or changing pigmented lesions should be evaluated for atypical features which could indicate a melanoma
- excisional biopsy should be considered if the lesion demonstrates rapid change, asymmetry, varied colours, irregular borders, and persistent pain or bleeding

OTHER ACQUIRED PIGMENTED LESIONS

Table 7. Comparison of Other Acquired Pigmented Lesions

	Clinical Features	Pathophysiology	Epidemiology	Differential Diagnosis	Clinical Course and Management
Atypical Nevus (Dysplastic Nevus)	Variegated macule/papule with irregular distinct melanocytes in the basal layer	Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus Often with region of adjacent nests	Five atypical nevi increase risk for melanoma Numerous dysplastic nevi may be part of familial atypical mole and melanoma syndrome Risk factor: family history	Melanoma	Follow with baseline photographs for changes Excisional biopsy if lesion changing or highly atypical Close surveillance with whole body skin examination
Ephelides (i.e. Freckles)	Small (<5 mm) well-demarcated light brown macules Sites: sun-exposed skin	Increased melanin within basal layer keratinocytes secondary to sun exposure	Skin phototypes I-II most commonly	Junctional nevi Juvenile lentigines	Multiply and darken with sun exposure, fade in winter No treatment required Sunscreen and sun avoidance may prevent the appearance of new freckles
Solar Lentigo (i.e. Liver Spot)	Well-demarcated brown/black macules Sites: sun-exposed skin	Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure	Most common in white individuals >40 yr Skin phototypes I-III most commonly	Lentigo maligna, seborrheic keratosis, pigmented AK	Laser therapy, cryotherapy
Becker's Nevus	Hairy, light brown macule/patch with a papular verrucous surface Sites: trunk and shoulders Onset in teen yr	Pigmented hamartoma with increased melanin in basal cells	M>F Often becomes noticeable at puberty	Hairy congenital melanocytic nevus	Hair growth follows onset of pigmentation Cosmetic management (usually too large to remove)
Melasma	Symmetrical hyperpigmentation on sun-exposed areas of face (forehead, upper lip, cheeks, chin)	Increase in number and activity of melanocytes Associated with estrogen and progesterone	F>M Common in pregnancy and women taking OCP or HRT Can occur with mild endocrine disturbances, antiepileptic medications, and other photosensitizing drugs Risk factors: sun exposure, dark skin tone	Post-inflammatory hyperpigmentation	Treatment: tinted mineral-based sunscreen hydroquinone, azelaic acid, retinoic acid, TCS, combination creams, destructive modalities (chemical peels), camouflage make-up. Very difficult to treat (can take months to improve)

Vascular Lesions

Table 8. Vascular Tumours Compared to Vascular Malformations

	Vascular Tumours	Vascular Malformations
Definition	Endothelial hyperplasia	Congenital malformation with normal endothelial turnover
Presence at Birth	Usually postnatal	100% at birth (not always obvious)
M:F	1:3-5	1:1
Natural History	Phases Proliferating Involuting Involuted	Proportionate growth (can expand)

HEMANGIOMAS

Clinical Features

- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a "bag of worms" when palpated

Pathophysiology

- benign vascular tumour
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

Table 9. Vascular Tumours

	Clinical Features	Pathophysiology	Epidemiology	Clinical Course	Management
Hemangioma of Infancy	Hot, firm, red to blue plaques or tumours	Benign vascular proliferation of endothelial lining	Appears shortly after birth; rarely congenital	Appears shortly after birth, increases in size over mo, then regresses 50% of lesions resolve spontaneously by 5 yr	10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis Consider treatment if not gone by school age; topical timolol, propranolol; systemic corticosteroids; laser treatment; surgery Provide early specialist referral or treatment in infants with high-risk hemangiomas
Spider Angioma (i.e. Campbell Telangiectasia)	Central red arteriole with slender branches, blanchable	Can be associated with hyperestrogenic state (e.g. in liver disease, pregnancy, OCP) but more often is not	Any age	Increase in number over time	Reassurance Electrodesiccation or laser surgery if patient wishes
Cherry Angioma (i.e. Campbell De Morgan Spot)	Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm Site: trunk Less friable compared to pyogenic granulomas	Benign vascular neoplasm	>30 y/o	Lesions do not fade in time Lesions bleed infrequently	Usually no treatment needed Laser or electrocautery for small lesions Excision of large lesions if necessary
Pyogenic Granuloma	Bright red, dome-shaped sessile or pedunculated friable nodule Sites: fingers, lips, mouth, trunk, toes DDx: glomus tumour, nodular MM, SCC, nodular BCC	Rapidly developing hemangioma Proliferation of capillaries with erosion of epidermis and neutrophilia	<30 y/o	Lesion grows rapidly over wk-mo, then stabilizes Lesion may persist indefinitely if untreated	Surgical excision with histologic examination Electrocautery; laser; cryotherapy

VASCULAR MALFORMATIONS

Table 10. Vascular Malformations

Type	Clinical Features	Pathophysiology	Management
Nevus Flammeus (i.e. Port-wine Stain)	Red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline Most common site: nape of neck Never spontaneously regresses but grows in proportion to the child	Congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution)	Laser or make-up
Nevus Simplex (i.e. Salmon Patch)	Pink-red irregular patches Midline macule on glabella known as "Angel Kiss;" in the nuchal region known as "Stork Bites" Present in 1/3 of newborns Majority regress spontaneously	Congenital dilation of dermal capillaries	No treatment required

Pyogenic granuloma is a misnomer: it is neither pyogenic nor granulomatous

Venous Lake: benign blue or violaceous papular lesion occurring on the face, lips, and ears due to dilation of a venule. Distinguished from malignant pigmented lesions through diascopy, as compression blanches the lesion

A spider angioma will blanch when the tip of a paperclip is applied to the centre of the lesion

Lipoma

Clinical Features
- single or multiple non-tender subcutaneous tumours that are soft and mobile
- occurs most frequently on the trunk and extremities, but can be anywhere on the body

Pathophysiology
- adipocytes enclosed in a fibrous capsule

Epidemiology
- often solitary or few in number, if multiple can be associated with rare syndromes

Differential Diagnosis
- angiolipoma, liposarcoma

Investigations
- biopsy only if atypical features (painful, rapid growth, firm)
- ultrasound

Management
- reassurance
- excision or liposuction only if desired for cosmetic purposes

Xanthoma

Clinical Features
- localized lipid deposits that manifest as papules, plaques, or nodules in the skin
- several variants: eruptive xanthoma (1-5 mm erythematous-to-yellow papules); tuberous xanthoma (≤3 cm yellow-to-orange or erythematous papules or nodules); tendinous xanthoma (smooth, firm, mobile, skin-coloured nodules); plane xanthoma (soft, yellow, thin plaques)

Pathophysiology
- xanthoma associated with hyperlipidemia: formed from macrophages due to excessive uptake and oxidation of low density lipoprotein particles
- xanthoma not associated with hyperlipidemia (e.g. plane xanthoma): develop associated with monoclonal gammopathy, multiple myeloma, and other hematologic diseases; immune complexes form between antibodies and lipoproteins leading to lipid accumulation in macrophages
- xanthoma not associated with hyperlipidemia (e.g. verruciform xanthoma): may be response to immune reaction to local trauma or inflammation

Epidemiology
- often present in adulthood (except xanthoma associated with hypercholesterolemia, in which xanthoma develops before 10 y/o)
- occur in both males and females, no sex predilection

Differential Diagnosis
- xanthelasma: sebaceous hyperplasia, juvenile xanthogranuloma, syringoma, nodular BCC
- plane xanthoma: necrobiotic xanthogranuloma
- eruptive xanthoma: generalized granuloma annulare, xanthoma disseminatum
- tendinous xanthoma and tuberous xanthoma: other nodular eruptions over joints and tendons (e.g. rheumatoid nodules, gouty tophi, subcutaneous granuloma annulare, erythema elevatum diutinum)
- verrucous xanthoma: condylomata, oral papillomas, verrucous carcinoma, SCC

Investigations
- biopsy (shave, punch, or excisional)
- fasting lipid panel (except for xanthomas not associated with hyperlipidemia, e.g. verruciform xanthomas)

Management
- typically asymptomatic and therefore do not require treatment unless for cosmetic reasons
- options include surgical excision, cryotherapy, trichloroacetic acid 70% chemical peels, or Er:YAG or Nd-YAG lasers
- pharmacologic treatment of dyslipidemia usually indicated

Treatment of Acne Scars
Tretinoin creams
Glycolic acid
Chemical peels for superficial scars
Injectable fillers (collagen, hyaluronic acid) for pitted scars
Laser

Topical Benzoyl Peroxide for Acne
Cochrane DB Syst Rev 2020:CD011154
Purpose: Determine the efficacy and safety of topical benzoyl peroxide for the treatment of acne.
Methods: Systematic review of 120 clinical trials (n=29,592) comparing the use of topical benzoyl peroxide for the treatment of clinically-diagnosed acne as compared to placebo or other topical medication.
Results: Benzoyl peroxide was more effective than placebo or no treatment in participant global self-assessment of acne improvement (RR 1.27; 95% CI, 1.12-1.45; low-certainty evidence). Little to no difference existed between benzoyl peroxide and adapalene (RR 0.99; 95% CI, 0.90-1.10) or clindamycin (RR 0.95; 95% CI, 0.68-1.34). Withdrawal due to adverse effects was higher with benzoyl peroxide than with no treatment, or placebo (RR 2.13; 95% CI, 1.55-2.93, low-certainty evidence) and the most common cited adverse effects included erythema, pruritus, and skin burning.
Conclusion: Benzoyl peroxide as monotherapy or add-on therapy may be more effective in the treatment of acne when compared to placebo, but not when compared to adapalene or clindamycin.

Acneiform Eruptions

Acne Vulgaris/Common Acne

Clinical Features
- a common inflammatory pilosebaceous disease categorized according to severity
  - Type I: comedonal, sparse, no scarring
  - Type II: comedonal, papular, moderate ± little scarring
  - Type III: comedonal, papular, and pustular, with scarring
  - Type IV: nodulocystic acne, risk of severe scarring
- sites of predilection: face, neck, upper chest, and back

Pathophysiology
- hyperkeratinization at the follicular ostia (opening) blocks the secretion of sebum leading to the formation of microcomedones
- androgens promote excess sebum production
- *Cutibacterium acnes* (*C. acnes*) metabolizes sebum to free fatty acids and produces pro-inflammatory mediators

Epidemiology
- age of onset typically in puberty (10-17 yr in females, 14-19 yr in males)
- in prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital adrenal hyperplasia)
- incidence decreases in adulthood
- genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

Differential Diagnosis
- folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

Table 11. Management of Acne

Compound/Drug Class	Product Names	Notes
MILD ACNE: OTC Topical Therapies		
Benzoyl peroxide (BPO)	Solugel®, Benzac®, Desquam®, Fostex®, CeraVe Acne Foaming Cleanser®	Helps prevent *Propionibacterium acnes* (*P. acnes*) resistance, is a bactericidal agent (targets *P. acnes*), and is comedolytic
Salicylic acid	CeraVe SA Cleanser	Used when patients cannot tolerate a topical retinoid due to skin irritation
MILD ACNE: Prescription Topical Therapies		
Antimicrobials	clindamycin (Dalacin T®), erythromycin	High rate of resistance when used as monotherapy
Retinoids	vitamin A acid (tretinoin, Stieva-A®, Retin A Micro®), adapalene (Differin®), ARAZLO® (tazarotene) Lotion 0.045%, AKLIEF® (trifarotene) Cream	Backbone of topical acne therapy All regimens should include a retinoid unless patient cannot tolerate
Combination products	clindamycin and BPO (Clindoxyl®) clindamycin and BPO (Benzaclin®) TactuPump® (adapalene and BPO) clindamycin and tretinoin (Biacna®)	Allows for greater adherence and efficacy Combines different mechanisms of action to increase efficacy and maximize tolerability
MODERATE ACNE		
Tetracycline/Minocycline/ Doxycycline	Sumycin®/Minocin®/Vibramycin®	Use caution with regard to drug interactions: do not use with isotretinoin Sun sensitivity Antibiotics require 3 mo of use before assessing efficacy
Cyproterone acetate-ethinyl estradiol	Diane-35®	After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance
Spironolactone	Aldactone®	May cause hyperkalemia if concurrent renal dx Black box warning for breast cancer
SEVERE ACNE		
Isotretinoin	Accutane®, Clarus®, Epuris®	See *Table 29, D53* for full side effect profile Most adverse effects are temporary and will resolve when the drug is discontinued Baseline lipid profile (risk of hypertriglyceridemia), LFTs and β-hCG before treatment May transiently exacerbate acne before patient sees improvement Refractory cases may require multiple courses of isotretinoin

Perioral Dermatitis

Clinical Features
- discrete erythematous papulopustular eruptions that often become confluent, forming inflammatory plaques on perioral, perinasal, and/or periorbital skin
- commonly symmetrical, rim of sparing around vermillion border of lips

Epidemiology
- 15-40 y/o, occasionally in younger children
- predominantly females

Differential Diagnosis
- contact dermatitis, rosacea, acne vulgaris

Management
- avoid all TCS, avoid ointment/oil-based products, stop all cosmetic products
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid
- systemic: doxycycline (utilized for its anti-inflammatory properties)
- occasional use of a topical calcineurin inhibitor cream (i.e. pimecrolimus)

Rosacea

Clinical Features
- dome-shaped inflammatory papules ± pustules
- flushing, non-transient erythema, and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks, and chin; rarely on scalp, neck, and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, spices
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration, and lymphedema in the skin can develop

Acne Myths Debunked
- Eating greasy food and chocolate does not cause or worsen acne
- Blackheads (comedones) are black because of oxidized fatty acids, not dirt
- Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator

Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo)

Acne Exacerbating Factors
- Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danazol
- Topical agents: TCS, tars, ointments, oily cosmetics
- Mechanical pressure or occlusion, such as leaning face on hands
- Emotional stress

A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone

Intralesional Injections
Intralesional steroids are effective in the cosmetic treatment of individual acne nodules

Isotretinoin and Pregnancy
- Use of isotretinoin during pregnancy is associated with spontaneous abortion and major birth defects such as facial dysmorphism and cognitive impairment
- Pregnancy should be ruled out before starting isotretinoin
- Patients should use two forms of contraception while on isotretinoin

Important Controversies Associated with Isotretinoin Therapy for Acne
Am J Clin Dermatol 2013;14:71-76
Main Points:
1. The evidence on whether isotretinoin causes depression and suicide is inconsistent; however, numerous controlled studies have shown an improvement in anxiety and depression scores in those taking isotretinoin.
2. There is no association between IBD and isotretinoin use. Only one study showed a significantly increased risk of UC. When considering using isotretinoin in a patient with IBD or with a strong family history, consider involving a gastroenterologist.

- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: blepharoconjunctivitis, keratitis, iritis

Pathophysiology
- unknown

Epidemiology
- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 y/o; F>M

Differential Diagnosis
- acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis

Management
- year round sunscreen
- avoid common triggers (e.g. alcohol, spicy food)
- telangiectasia: treated by vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; paring, electrosurgery, cryotherapy, laser therapy (CO_2, argon, Nd:YAG)

Table 12. Specific Rosacea Treatments

First Line	Second Line	Third Line
Oral tetracyclines Topical metronidazole Oral erythromycin (250-500 mg PO bid) Topical azelaic acid Topical ivermectin	Topical clindamycin Oral metronidazole	Oral retinoids

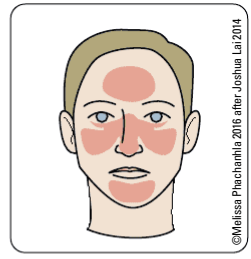

Figure 7. Rosacea distribution

Rosacea can be differentiated from acne by the absence of comedones, a predilection for the central face, and symptoms of flushing

Guidelines for the Diagnosis of Rosacea
J Drugs Dermatol 2012;11(6):725-730

Presence of one or more of the following primary features:
- Flushing (transient erythema)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

May include one or more of the following secondary features:
- Burning or stinging
- Dry appearance
- Edema
- Phymatous changes
- Ocular manifestations
- Peripheral location

Dermatitis (Eczema)

Definition
- inflammation of the skin

Clinical Features
- poorly demarcated erythematous plaques
- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting, excoriations
- chronic dermatitis: lichenification, xerosis, fissuring

Asteatotic Dermatitis

Clinical Features
- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (i.e. "winter itch") but starts in the fall
- shins predominate, looks like a "dried river bed"

Management
- skin rehydration with moisturizing routine (products with urea) ± TCS

Atopic Dermatitis

Clinical Features
- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution depends on age
- inflammation, lichenification, and excoriations are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with: keratosis pilaris (hyperkeratosis of hair follicles, "chicken skin"), xerosis, occupational hand dryness
- associated with severe or poorly controlled psychosocial distress and psychiatric comorbidities

Epidemiology
- frequently affects infants, children, and young adults
- 10-20% of children <5 yr in developed countries are affected
- associated with personal or family history of atopy (asthma, allergic rhinitis), anaphylaxis, eosinophilia
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

Pathophysiology
- a T-cell driven inflammatory process with epidermal barrier dysfunction

Emollients and Moisturisers for Eczema
Cochrane DB Syst Rev 2017:CD012119
Purpose: To review the effects of moisturizers for eczema.
Methods: This review included 77 RCTs (n=6603) published prior to December 2015 on the effects of moisturizer on eczema.
Results: Moisturizers were more effective at reducing patient-reported eczema (RR 2.46; 95% CI, 1.16 to 5.23; low-quality evidence), itch (SMD -1.10; 95% CI, -1.83 to -0.38), investigator-assessed disease severity scores (SMD -1.04; 95% CI, -1.57 to -0.51; high-quality evidence), and flares (RR 0.33; 95% CI, 0.17 to 0.62; moderate-quality evidence), with no effect on adverse events (RR 1.03; 95% CI, 0.82 to 1.30; moderate-quality evidence).
Conclusion: Moisturizers are beneficial for eczema symptoms and severity. Greater benefits are observed when combined with active treatments. Evidence does not support the use of one moisturizer over another.

Triggers for Atopic Dermatitis
- Irritants (fragrance, detergents, solvents, clothing, water hardness)
- Contact allergens
- Inappropriate bathing habits (e.g. long hot showers)
- Sweating
- Microbes (e.g. *S. aureus*)
- Stress

Investigations

- clinical diagnosis
- consider: skin biopsy, serum IgE levels, patch testing if allergic contact dermatitis is suspected

Management

- goal: reduce signs and symptoms, prevent or reduce recurrences/flares
- better outcomes (e.g. fewer flare-ups, modified course of disease) if diagnosis made early
- avoid triggers of AD (e.g. wool, fragrance, heat, etc.)
- be vigilant for depressive symptoms and the possible need for psychiatric referral, especially among those with severe disease
- non-pharmacologic therapy
  - moisturizers
    - apply liberally and reapply at least daily
    - bathe in plain warm water for a short period of time once daily followed by lightly, but not completely, drying the skin with a towel; immediately apply topical agents or moisturizers after this
  - use fragrance-free hypoallergenic non-soap cleansers
- pharmacologic therapy
  - topical corticosteroids
    - effective in reducing acute and chronic symptoms as well as prevention of flares
    - choice of steroid potency depends on age, body site, short vs. long-term use
    - apply one adult fingertip unit (0.5 g) to an area the size of two adult palms bid for at least 14 days for acute flares
    - most common local side effects: skin atrophy, purpura, telangiectasia, striae, and acneiform eruption
    - rare local side effects: hypopigmentation (more commonly seen in patients of colour, especially with higher potency TCS), hypertrichosis
  - topical calcineurin inhibitors
    - tacrolimus 0.03%, 0.1% (Protopic®) and pimecrolimus 1% (Elidel®)
    - can be used as acute treatments and as steroid-sparing agents in the long-term
    - advantages over long-term corticosteroid use: no skin atrophy; safe for sensitive areas such as the face and neck
    - apply bid for acute flares, and 2-3x/wk to recurrent sites to prevent relapses
    - local side effects: stinging, burning, cost
  - topical PDE-4 inhibitors
    - crisaborole (Eucrisa®)
  - topical small molecules
    - ruxolitinib (JAK-1/2 inhibitor) (OpzeluraTM)
  - oral small molecules
    - upadacitinib (JAK-1 inhibitor) (Rinvoq®)
    - abrocitinib (JAK-1 inhibitor) (Cibinqo®)
  - biologics
    - dupilumab (anti-IL 4/13) (Dupixent®)
    - tralokinumab (anti-IL 13) (Adtralza®)

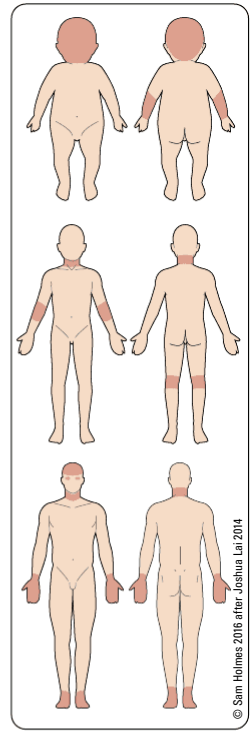

Figure 8. AD distribution
The typical distribution of AD in infants <6 mo (top), children >18 mo (middle), and adults ≥18 yr (bottom)

Complications

- infections
  - treatment of infections:
    - topical mupirocin, ozenoxacin, or fusidic acid (Canada only, not available in US)
    - oral antibiotics (e.g. cloxacillin, cephalexin) for widespread S. aureus infections

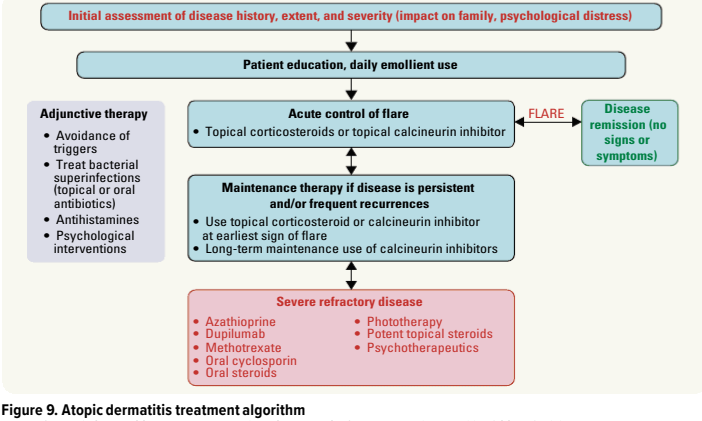
Initial assessment of disease history, extent, and severity (impact on family, psychological distress)
Patient education, daily emollient use
Adjunctive therapy
• Avoidance of triggers
• Treat bacterial superinfections (topical or oral antibiotics)
• Antihistamines
• Psychological interventions
Acute control of flare
• Topical corticosteroids or topical calcineurin inhibitor
FLARE
Disease remission (no signs or symptoms)
Maintenance therapy if disease is persistent and/or frequent recurrences
• Use topical corticosteroid or calcineurin inhibitor at earliest sign of flare
• Long-term maintenance use of calcineurin inhibitors
Severe refractory disease
• Azathioprine
• Dupilumab
• Methotrexate
• Oral cyclosporin
• Oral steroids
• Phototherapy
• Potent topical steroids
• Psychotherapeutics

Figure 9. Atopic dermatitis treatment algorithm
Adapted from: Ellis C, et al. ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. Br J Dermatol 2003;148(Suppl 63):3-10

Contact Dermatitis

Clinical Features
- cutaneous inflammation caused by an external agent(s)

Table 13. Contact Dermatitis

	Irritant Contact Dermatitis	Allergic Contact Dermatitis
Mechanism of Reaction	Toxic injury to skin; non-immune mechanism	Cell-mediated delayed (Type IV) hypersensitivity reaction (see Rheumatology, RH2)
Type of Reaction	Erythema, dryness, fine scale, burning Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure) Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common	Erythema with a papulovesicular eruption, swelling, pruritus
Frequency	Majority; will occur in anyone given sufficient concentration of irritants	Minority; patient acquires susceptibility to allergen that persists indefinitely
Distribution	Hands are the most common site	Areas exposed to allergen
Examples	Soaps, weak alkali, detergents, organic solvents, alcohol, oils	Many allergens are irritants, so may coincide with irritant dermatitis Nickel Tattoos
Management	Avoidance of irritants Barrier moisturizers Topical/oral steroids	Patch testing to determine specific allergen Avoid allergen and its cross-reactants TCS bid prn Systemic steroids prn if extensive

Dyshidrotic Dermatitis

Clinical Features
- "tapioca pudding" papulovesicular or bullous dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infections common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

Pathophysiology
- unknown
- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate flares

Management
- topical: high potency TCS with plastic cling wrap occlusion to increase penetration
- systemic
  - prednisone in severe cases
  - alitretinoin (Toctino®) for all types of chronic hand dermatitis, including dyshidrotic dermatitis
  - antibiotics for secondary *S. aureus* infection

Nummular Dermatitis

Clinical Features
- nummular (coin-shaped), pruritic, dry, scaly, erythematous plaques
- secondary infection common

Pathophysiology
- little is known, but it is often accompanied by xerosis, which results from a dysfunction of the epidermal lipid barrier; this in turn can allow permeation of environmental agents, which can induce an allergic or irritant response

Management
- moisturization
- mid-high potency TCS ointment bid

Seborrheic Dermatitis

Clinical Features
- greasy, erythematous, yellow, scaling, papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: "cradle cap"

- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, nasolabial folds, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

Pathophysiology
- possible etiologic association with *Malassezia spp*. (yeast)

Epidemiology
- common in infants, adolescents, and males
- increased incidence and severity in immunocompromised patients and Parkinson's disease
- in adults can cause dandruff (pityriasis sicca)
- can overlap with psoriasis

Management
- face: ketoconazole (Ketoderm) cream bid prn and/or mild steroid cream bid prn
- scalp: ketoconazole 2% shampoo (Nizoral®), ciclopirox (Stieprox®) shampoo, selenium sulfide (e.g. Dercos Anti-Dandruff Shampoo® or Head and Shoulders Clinical Strength®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)

Stasis Dermatitis

Clinical Features
- erythematous, scaly, pruritic plaques on lower legs, particularly the medial ankle
- brown hemosiderin deposition, woody fibrosis, and lipodermatosclerosis in late stages
- usually bilateral, accompanied by swelling, oozing, crusting, may have accompanying varicosities

Pathophysiology
- chronic venous insufficiency leads to venous stasis
- surrounding soft tissue inflammation and fibrosis results

Investigations
- Doppler if suspicious for DVT, other vascular studies (e.g. venous duplex, ankle-brachial index)
- swab for bacterial culture if there is crusting

Management
- compression stockings are the most important therapy (if no peripheral arterial disease)
- rest and elevate legs
- moisturizer daily after shower to treat xerosis
- mid-high potency TCS to control inflammation

Complications
- ulceration (common at medial malleolus), secondary bacterial infections

Lichen Simplex Chronicus

Clinical Features
- well-defined plaque(s) of lichenified skin with increased pruritic skin markings ± excoriations
- common sites: neck, scalp, extremities, urogenital area
- often seen in patients with atopy, anxiety disorders, nonspecific emotional stress, among other conditions

Pathophysiology
- skin hyperexcitable to itch, resulting in continued rubbing/scratching of skin
- eventually lichenification occurs

Investigations
- histopathology/biopsy confirms diagnosis if clinical diagnosis uncertain
- if patient has generalized pruritus, rule out systemic cause: CBC with differential count, transaminases, bilirubin, ferritin, renal and thyroid function tests, TSH, glucose, SPEP
- CXR if lymphoma suspected

Management
- antipruritics (e.g. topical pramoxine hydrochloride, topical or intralesional steroids)

Papulosquamous Diseases

Lichen Planus

The 6 Ps of Lichen Planus
Purple
Pruritic
Polygonal
Peripheral
Papules
Penis (i.e. mucosa)

Clinical Features
- acute or chronic inflammation of skin or mucous membranes
- morphology: pruritic, well-demarcated, violaceous, polygonal, flat-topped papules and plaques
- common sites: wrists, nails, scalp, mucous membranes in 60% (mouth, vulva, glans)
- distribution: symmetrical and bilateral
- Wickham's striae: lacy, whitish reticular network mostly seen on oral mucosa; pathognomonic but may not be present
- other mucous membrane lesions: milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging, pterygium formation, complete dystrophy
- scalp: known as lichen planopilaris, scarring alopecia with perifollicular hyperkeratosis and erythema
- usually resolves spontaneously but may last for wk, mo, or yr
- rarely associated with hepatitis C
- Koebner phenomenon

Pathophysiology
- immune-mediated, antigen unknown
- lymphocyte activation leads to keratinocyte apoptosis

Epidemiology
- 1%, 30-60 yr, F>M

Investigations
- consider a skin biopsy
- hepatitis C serology if patient has risk factors

Management
- topical or intralesional steroids
- short courses of oral prednisone (rarely)
- phototherapy, oral retinoids, or systemic immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine) for extensive or recalcitrant cases

Pityriasis Rosea

Clinical Features
- acute, self-limiting eruption characterized by red or flesh-coloured oval plaques/patches with central scale that does not extend to edge of lesion
- lesions in darker skin tones may appear dusky violet or red-brown, and leave lingering hypo-/hyperpigmentation after the eruption clears
- long axis of lesions follows skin tension lines (i.e. Langer lines) parallel to ribs producing "Christmas tree" pattern on back
- varied degree of pruritus
- most start with a "herald" patch which precedes other lesions by 1-2 wk
- common sites: trunk, proximal aspects of arms and legs

Pathophysiology
- suspected HHV-7 or HHV-6 reactivation

Investigations
- none required

Management
- none required; clears spontaneously in 6-12 wk
- symptomatic: topical corticosteroids if pruritic, cool compresses, emollients

Skin Treatments for Chronic Plaque Psoriasis
Cochrane DB Syst Rev 2013:CD005028
Purpose: To review the effectiveness, tolerability, and safety of topical treatments for chronic plaque psoriasis.
Methods: This review identified RCTs comparing active topical treatments to either placebo or vitamin D analogues (used alone or in combination) in people with chronic plaque psoriasis.
Results: 170 studies including a total of 34808 participants were included in this review.
Conclusion: Both topical corticosteroids and vitamin D analogues were effective in treating chronic plaque psoriasis of the body. Corticosteroids showed benefits over vitamin D analogues in treating chronic plaque psoriasis of the scalp. Treatments combining vitamin D analogues and topical corticosteroids were more effective than using either vitamin D analogues or corticosteroids alone. Vitamin D analogues did result in more local adverse events than topical corticosteroids, the most common event being skin irritation or burning. People were more likely to discontinue using vitamin D analogues than topical corticosteroids.

Psoriasis

Classification
1. plaque psoriasis 2. guttate psoriasis 3. erythrodermic psoriasis
4. pustular psoriasis 5. inverse psoriasis

Pathophysiology
- not fully understood, genetic and immunologic factors
- shortened keratinocyte cell cycle correlates with Th1- and Th17-mediated inflammatory response

Epidemiology
- 1.5-2%, M=F
- all ages: peaks of onset: 20-39 yr and 50-60 yr
- polygenic inheritance: 8% with one affected parent, 41% with both parents affected
- risk factors: smoking, obesity, alcohol, drugs, infections, physical trauma (Koebner phenomenon)

Differential Diagnosis
- mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea corporis, nummular dermatitis, contact dermatitis, lichen planus, secondary syphilis, DLE

Investigations
- none required; biopsy if atypical presentation

PLAQUE PSORIASIS

Clinical Features
- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- often worse in winter (lack of sun)
- Auspitz sign: pinpoint bleeding observed when scale is removed
- common sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

Management
- depends on severity of disease, as defined by BSA affected or PASI
- mild (BSA <3%, PASI <3)
  - first line treatment includes TCS ± topical vitamin D analogue combination
  - topical retinoid ± TCS combination tends to be less tolerated than first line therapies
  - emollients
  - roflumilast
  - anthralin and tar are rarely used
  - phototherapy or systemic treatment may be necessary if the lesions are scattered or in difficult-to-treat areas (e.g. palms, soles, scalp, and genitals)
- moderate (BSA 3-10%, PASI 3-10) to severe (BSA >10%, PASI >10)
  - phototherapy if accessible
  - systemic or biological therapy based on patient's treatment history and comorbidities
  - TCS ± topical vitamin D3 analogue as adjunct therapy

Table 14. Topical Treatment of Psoriasis

Treatment	Mechanism	Comments
Emollients	Reduce fissure formation	
Salicylic acid 1-12%	Remove scales	
Tar (LCD: liquor carbonis detergens)	Inhibit DNA synthesis, increase cell turnover	Messy, poor long-term compliance
Topical corticosteroids	Reduce scaling, redness and thickness	Use appropriate potency steroid in different areas for degree of psoriasis
Vitamin D analogues: calcipotriene/ calcipotriol (Dovonex®, Silkis®)	Reduce keratinocyte hyperproliferation	
Betamethasone + calcipotriene (Dovobet®)	Combined TCS and vitamin D analogue. See above mechanisms	Not to be used on face or folds
Retinoid: Tazarotene (Tazorac®) (gel/cream)	Vitamin A derivative, reduce scaling	Irritating
Halobetasol propionate + tazarotene (Duobrii™) (lotion)	Combined TCS and vitamin A derivative, reduce scaling and inflammation	Irritating
PDE-4 inhibitor: Roflumilast (Zoryve™) (cream)	Reduce inflammation	Steroid sparing, can be used on face or folds

Table 15. Systemic Treatment of Psoriasis

Treatment	Considerations	Adverse Effects
Acitretin	More effective when used in combination with phototherapy	Alopecia, cheilitis, teratogenicity, hepatotoxicity, photosensitivity, epistaxis, xerosis, hypertriglyceridemia
Cyclosporine	Used for intermittent control rather than continuously Avoid using for >1 yr Non-melanoma skin cancer risk higher when combined with PUVA	Renal toxicity, hypertension, hypertriglyceridemia, immunosuppression, lymphoma, non-melanoma skin cancer
Methotrexate	Has been used for over 50 yr	Bone marrow toxicity, hepatic cirrhosis, teratogenicity
Apremilast (Otezla®)	Extremely safe	GI upset, headache, loose stool, weight loss
Deucravacitinib (Sotyktu™)	More effective than apremilast Well tolerated	Acne, increased risk of infection
PUVA	Highly effective in achieving remission Avoid >200 sessions in lifetime	Burning, skin cancer
Broadband UVB and NB-UVB (311 nm)	UVB is much less carcinogenic than PUVA. NB-UVB has not been shown to increase the risk of skin cancer	Rare burning

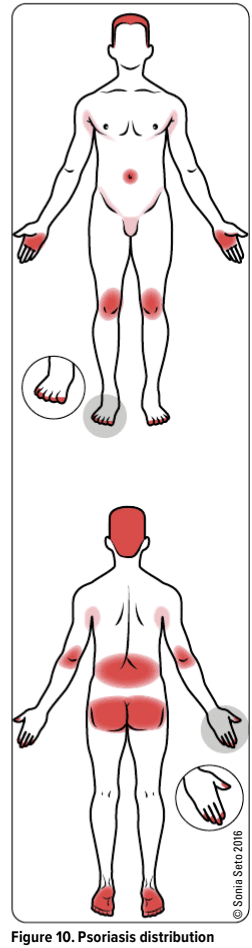

Figure 10. Psoriasis distribution

Mechanism of Biologics
"-mab" = monoclonal antibody
"-cept" = receptor

Table 16. Biologics Approved in Canada

Treatment	Route	Dosing Schedule	Effectiveness	Action
Etanercept (Enbrel®)*	SC	50 mg twice per wk for 3 mo, then 50 mg every wk	+++	Anti-TNF
Adalimumab (Humira®)*	SC	80 mg x 1, then 40 mg at wk 1, and every 2 wk thereafter	++++	Anti-TNF
Infliximab (Remicade®)*	IV	5 mg/kg at wk 0, 2, 6, and every 8 wk thereafter	+++++	Anti-TNF
Ustekinumab (Stelara®)*	SC	45 mg or 90 mg at wk 0, 4, and every 12 wk thereafter	++++	Anti-IL 12/23
Secukinumab (Cosentyx®)*	SC	300 mg at wk 0, 1, 2, 3, 4, and every mo thereafter	+++++	Anti-IL 17A
Ixekizumab (Taltz®)*	SC	160 mg at wk 0, then 80 mg at wk 2, 4, 6, 8, 10, 12, then 80 mg every 4 wk thereafter	+++++	Anti-IL 17A
Guselkumab (Tremfya®)*	SC	100 mg at wk 0, 4, and every 8 wk thereafter	+++++	Anti-IL 23
Brodalumab (Siliq®)	SC	210 mg at wk 0, 1, 2 and every 2 wk thereafter	+++++	Anti-IL 17RA (targets IL 17 receptor subunit A, rather than IL 17A itself)
Certolizumab pegol (Cimzia®)*	SC	400 mg every 2 wk	++++	Anti-TNF
Risankizumab (Skyrizi®)*	SC	150 mg at wk 0, 4, and every 12 wk thereafter	+++++	Anti-IL 23
Tildrakizumab (ILUMYA®)	SC	100 mg at wk 0, 4, and every 12 wk thereafter	++++	Anti-IL 23
Bimekizumab (BIMZELX®)	SC	320 mg at wk 0, 4, 8, 12, 16, and every 8 wk thereafter	+++++	Anti-IL 17A/IL 17F
Spesolimab (SPEVIGO®)**	IV	900 mg x 1 at wk 0, and if symptoms persist 900 mg x 1 at wk 1	n/a***	Anti-IL 36R

*Can also be used to treat psoriatic arthritis **Approved for generalized pustular psoriasis only ***Efficacy comparison not available

GUTTATE PSORIASIS ("RAIN DROP-LIKE")

Clinical Features
- discrete, scattered salmon-pink small scaling papules
- sites: diffuse, usually on trunk and legs, sparing palms and soles
- often antecedent streptococcal pharyngitis

Management
- UVB phototherapy, sunlight, emollients, TCS
- penicillin V, erythromycin, or azithromycin if GAS on throat culture

ERYTHRODERMIC PSORIASIS

Clinical Features
- generalized erythema (>90% of BSA) with fine desquamative scale on surface
- associated signs and symptoms: arthralgia, pruritus, dehydration, electrolyte imbalance
- aggravating factors: lithium, β-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

Management
- potentially life-threatening, requires immediate medical care
- IV fluids, monitor fluids and electrolytes, may require hospitalization
- treat underlying aggravating condition
- cyclosporine, acitretin, methotrexate, UV, biologics

PUSTULAR PSORIASIS

Clinical Features
- sudden onset of erythematous macules and papules which evolve rapidly into pustules, can be painful
- may be generalized or localized
- patient can have a history of psoriasis; may occur with sudden withdrawal from steroid therapy

Management
- methotrexate, cyclosporine, acitretin, UV, biologics

INVERSE PSORIASIS

Clinical Features
- erythematous plaques on flexural surfaces such as axillae, inframammary folds, gluteal fold, inguinal folds
- lesions may be macerated

Management
- low potency TCS
- topical vitamin D analogues (e.g. calcipotriene, calcitriol)
- topical calcineurin inhibitors (e.g. tacrolimus, pimecrolimus)
- topical PDE-4 inhibitors (e.g. roflumilast)
- phototherapy

PSORIATIC ARTHRITIS
- 20-30% of patients with psoriasis also suffer from psoriatic arthritis
- psoriatic patients with nail or scalp involvement are at a higher risk for developing psoriatic arthritis
- see Rheumatology, RH25

Vesiculobullous Diseases

Bullous Pemphigoid

Clinical Features
- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- can present as urticarial plaques without bullae
- common sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth in 33%

Pathophysiology
- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leading to subepidermal bullae

Epidemiology
- mean age of onset: 60-80 yr, F=M

Investigations
- immunofluorescence shows linear deposition of IgG and C3 along the basement membrane
- anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

Prognosis
- he als without scarring, usually chronic
- rarely fatal

Management
- prednisone 0.5-1 mg/kg/d until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclosporine, mycophenolate mofetil)
- potent TCS (clobetasol) may be as effective as systemic steroids in limited disease
- tetracycline ± nicotinamide is effective for some cases
- immunosuppressants such as azathioprine, mycophenolate mofetil, cyclosporine
- For refractory cases: IVIg, rituximab, dupilumab, or omalizumab

Pemphigus Vulgaris

Clinical Features
- autoimmune blistering disease characterized by flaccid, non-pruritic intraepidermal bullae/vesicles on an erythematous or normal skin base
- may present with erosions and secondary bacterial infection
- sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
- Nikolsky's sign: epidermal detachment with shear stress
- Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

Pemphigus Vulgaris vs. Bullous Pemphigoid
Vulgari**S** = **S**uperficial, intraepidermal, flaccid lesions
Pemphigoi**D** = **D**eeper, tense lesions at the dermal-epidermal junction

Pathophysiology
- IgG against epidermal desmoglein-1 and -3 lead to loss of intercellular adhesion in the epidermis

Epidemiology
- 40-60 yr, M=F, higher prevalence in Jewish, Mediterranean, Asian populations
- paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine

Pemphigus Foliaceus
An autoimmune intraepidermal blistering disease that is more superficial than pemphigus vulgaris due to antibodies against desmoglein-1, a transmembrane adhesion molecule. Appears as crusted patches, erosions and/or flaccid bullae that usually start on the trunk. Localized disease can be managed with TCS. Active widespread disease is treated like pemphigus vulgaris

Investigations
- immunofluorescence: shows intraepidermal IgG and C3 deposition
- circulating serum anti-desmoglein IgG antibodies

Prognosis
- lesions heal with hyperpigmentation but do not scar
- may be fatal unless treated with immunosuppressive agents

Management
- prednisone 1-2 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclophosphamide, cyclosporine, IVIg, mycophenolate mofetil, rituximab)

Dermatitis Herpetiformis

Clinical Features
- grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging, excoriations
- lesions grouped, bilaterally symmetrical
- common sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

Pathophysiology
- transglutaminase IgA deposits in the skin alone or in immune complexes leading to eosinophil and neutrophil infiltration
- almost all carry HLA-DQ2 or DQ8, other haplotypes include B8, DR3, and DQWZ
- 90% have gluten-sensitive enteropathy, 20% have intestinal symptoms of celiac disease
- 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

Epidemiology
- 20-60 yr, M:F=2:1

Investigations
- biopsy
- immunofluorescence shows IgA deposits in perilesional skin

Management
- dapsone (sulfapyridine if contraindicated or poorly tolerated)
- gluten-free diet for life: this can reduce risk of lymphoma

Porphyria Cutanea Tarda

Clinical Features
- skin fragility followed by formation of tense vesicles/bullae and erosions on photo-exposed skin
- gradual healing to scars, milia
- periorbital violaceous discolouration, diffuse hypermelanosis, facial hypertrichosis
- common sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

Pathophysiology
- uroporphyrinogen decarboxylase deficiency leads to excess heme precursors
- can be associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

Epidemiology
- 30-40 yr, M>F

Investigations
- urine and HCl 5% shows orange-red fluorescence under Wood's lamp (UV rays)
- 24 h urine has elevated uroporphyrins
- stool contains elevated coproporphyrins
- immunofluorescence shows IgE at dermal-epidermal junctions

Management
- discontinue aggravating substances (alcohol, estrogen therapy)
- phlebotomy to decrease body iron load
- low dose hydroxychloroquine

Drug Eruptions

Exanthematous

EXANTHEMATOUS DRUG REACTION

Clinical Features
- morphology: erythematous macules and papules ± scale
- spread: symmetrical, trunk to extremities
- time course: 7-14 d after drug initiation, fades 7-14 d after withdrawal

Diagnosis of a Drug Reaction
Classification by Naranjo et al. has 4 criteria:
1. Temporal relationship between drug exposure and reaction
2. Recognized response to suspected drug
3. Improvement after drug withdrawal
4. Recurrence of reaction on re-challenge with the drug

Definite drug reaction requires all 4 criteria to be met
Probable drug reaction requires #1-3 to be met
Possible drug reaction requires only #1

Epidemiology
- most common cutaneous drug reaction; increased in presence of infections
- common causative agents: penicillin, sulfonamides, phenytoin

Management
- weigh risks and benefits of drug discontinuation
- antihistamines, emollients, TCS

Drug Hypersensitivity Syndrome Triad
Fever
Exanthematous eruption
Internal organ involvement

DRUG-INDUCED HYPERSENSITIVITY SYNDROME (DIHS)/DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Clinical Features
- morphology: morbilliform rash involving face, trunk, arms; can have facial edema
- systemic features: fever, malaise, cervical lymphadenopathy, internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- spread: starts with face or periorbitally and spreads caudally; no mucosal involvement
- time course: onset 1-6 wk after first exposure to drug; persists wk after withdrawal of drug

Epidemiology
- rare: incidence varies considerably depending on drug
- common causative agents: anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, lamotrigine), sulfonamides, and allopurinol
- 10% mortality if severe, undiagnosed, and untreated

Management
- discontinue offending drug ± prednisone 0.5 mg/kg/d, consider cyclosporine in severe cases
- may progress to generalized exfoliative dermatitis/erythroderma if drug is not discontinued

Urticarial

DRUG-INDUCED URTICARIA AND ANGIOEDEMA

Clinical Features
- morphology: wheals lasting >24 h unlike non-drug induced urticaria, angioedema (face and mucous membranes)
- systemic features: may be associated with systemic anaphylaxis (bronchospasm, laryngeal edema, shock)
- time course: h-d after exposure depending on the mechanism

Epidemiology
- second most common cutaneous drug reaction
- common causative agents: penicillins, ACEi, analgesics/anti-inflammatories, radiographic contrast media

Management
- discontinue offending drug, treatment with antihistamines, oral corticosteroids, epinephrine if anaphylactic

SERUM SICKNESS-LIKE REACTION

Clinical Features
- morphology: symmetrical cutaneous eruption (usually urticarial)
- systemic features: malaise, low grade fever, arthralgia, lymphadenopathy
- time course: appears 1-3 wk after drug initiation, resolves 2-3 wk after withdrawal

Epidemiology
- more prevalent in children (0.02-0.2%)
- common causative agents: cefaclor in children; bupropion in adults

Management
- discontinue offending drug ± topical/oral corticosteroids

Pustular

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)

Clinical Features
- morphology: extensive erythematous, edematous, and sterile pustules
- systemic features: high fever, leukocytosis with neutrophilia
- spread: starts in face and intertriginous areas, spreads to trunk and extremities
- time course: appears 1 wk after drug initiation, resolves 2 wk after withdrawal

Epidemiology
- rare: 1-5/million
- common causative agents: aminopenicillins, cephalosporins, clindamycin, calcium channel blockers

Management
- discontinue offending drug and systemic corticosteroids

Bullous

STEVENS-JOHNSON SYNDROME (SJS)/TOXIC EPIDERMAL NECROLYSIS (TEN)

Clinical Features
- morphology: prodromal rash (morbilliform/targetoid lesions ± purpura, or diffuse erythema), confluence of flaccid blisters, positive Nikolsky sign (epidermal detachment with shear stress), full thickness epidermal loss; dusky tender skin, bullae, desquamation/skin sloughing, atypical targets
- classification:
  - BSA with epidermal detachment: <10% in SJS, 10-30% in SJS/TEN overlap, and >30% in TEN
- spread: face and extremities; may generalize; scalp, palms, soles relatively spared; erosion of mucous membranes (lips, oral mucosa, conjunctiva, GU mucosa)
- systemic features: fever (higher in TEN), cytopenias, renal tubular necrosis/AKI, tracheal erosion, infection, contractures, corneal scarring, phimosis, vaginal synechiae
- time course: appears 1-3 wk after drug initiation; progression <4 d; epidermal regrowth in 3 wk
- can have constitutional symptoms: malaise, fever, hypotension, tachycardia

Epidemiology
- SJS: 1.2-6/million; TEN: 0.4-1.2/million
- risk factors: SLE, HIV/AIDS, HLA-B1502 (reaction most prevalent in East Asians, associated with carbamazepine), HLA-B5801 (reaction most prevalent in Asian and White populations, associated with allopurinol)
- common causative agents: drugs (allopurinol, anti-epileptics, sulfonamides, NSAIDs, cephalosporins, immune checkpoint inhibitors) responsible in 50% of SJS and 80% of TEN; viral or mycoplasma infections
- prognosis: 5% mortality in SJS, 30% in TEN due to fluid loss and infection

Differential Diagnosis
- scarlet fever, phototoxic eruption, GVHD, SSSS, exfoliative dermatitis, AGEP, paraneoplastic pemphigus

Management
- discontinue offending drug
- admit to intermediate/intensive care/burn unit
- supportive care: IV fluids, electrolyte replacement, nutritional support, pain control, wound care, sterile handling, monitor for and treat infection
- IVIg, cyclosporine, corticosteroids, or etanercept

SCORTEN Score for TEN Prognosis
One point for each of: age ≥40, malignancy, initial BSA detached ≥10%, tachycardia ≥120 bpm, serum urea >10 mmol/L, serum glucose >14 mmol/L, serum bicarbonate <20 mmol/L

Used to determine appropriate clinical setting: score 0-1 can be treated in non-specialized wards; score ≥2 should be transferred to intensive care or burn unit

Score at admission is predictive of survival: 94% for 0-1, 87% for 2, 53% for 3, 25% for 4, and 17% for ≥5

Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis
JAMA Dermatol 2017;153:514-522
Purpose: To examine possible immunomodulating treatments for SJS/TEN and estimate mortality effect compared to supportive care.
Methods: Systematic review of randomized and nonrandomized studies on systemic immunomodulating therapies or supportive care for SJS/TEN.
Results: Ninety-six studies with 3248 patients were included in the final analysis. Glucocorticoids were associated with a survival benefit for patients (aggregate - OR 0.5, 95% CI 0.3-1.01). Though findings were limited to a small number of patients overall, cyclosporine was associated with significant benefit (OR 0.1; 95% CI 0.0-0.4). No beneficial effects were observed with other therapies, including IVIg.
Conclusion: Though based on limited evidence, glucocorticoids and cyclosporine were the most promising as SJS/TEN immunosuppressive therapies.

Other

FIXED DRUG ERUPTION

Clinical Features
- morphology: sharply demarcated erythematous oval patches on the skin or mucous membranes
- spread: commonly face, mucosa, genitalia, acral; recurs in same location upon subsequent exposure to the drug (fixed location)

Epidemiology
- common causative agents: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein

Management
- discontinue offending drug ± prednisone 1 mg/kg/d x 2 wk for generalized lesions
- potent TCS for non-eroded lesions or antimicrobial ointment for eroded lesions

PHOTOSENSITIVITY REACTION

Clinical Features
- phototoxic reaction: "exaggerated sunburn" (erythema, edema, vesicles, bullae) confined to sun-exposed areas
- photoallergic reaction: pruritic eczematous eruption with papules, vesicles, scaling, and crusting that may spread to areas not exposed to light

Pathophysiology
- phototoxic reaction: direct tissue injury
- photoallergic reaction: type IV delayed hypersensitivity

Epidemiology
- common causative agents: chlorpromazine, doxycycline, thiazide diuretics, procainamide

Management
- sun protection ± topical/oral corticosteroids

Heritable Disorders

Ichthyosis Vulgaris

Clinical Features
- xerosis with fine scaling as well as large adherent scales ("fish-scales")
- affects arms, legs, palms, soles, back, forehead, and cheeks; spares flexural creases
- improves in summer, with humidity, and as the child grows into adulthood

Pathophysiology
- genetic deficiency in filaggrin protein leads to abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

Epidemiology
- 1:300 incidence
- autosomal dominant inheritance
- associated with AD and keratosis pilaris

Investigations
- electron microscopy: keratohyalin granules

Management
- immersion in bath and oils followed by an emollient cream, humectant cream, or creams/oil containing urea or α- or β-hydroxy acids
- intermittent systemic retinoids for severe cases

Epidermolysis Bullosa

Clinical Features
- blisters and erosions on skin and mucous membranes following minor trauma
- extracutaneous manifestation may occur in severe disease and include intraoral blistering and erosions, nail abnormalities, esophageal strictures, and genitourinary abnormalities

Pathophysiology
- group of rare inherited diseases caused by mutations in genes coding for structural proteins involved in basement membrane of skin

Differential Diagnosis
- friction blisters, epidermolysis bullosa acquisita

Investigations
- skin biopsy for immunofluorescence mapping

Management
- symptomatic management including supportive wound care
- avoid inducing friction on skin
- place padding on furniture
- wear loose clothing and appropriate footwear
- maintain cool ambient room temperature

Neurofibromatosis (Type I; von Recklinghausen's Disease)

Clinical Features
- diagnostic criteria includes 2 or more of the following, if parent not diagnosed with NF1:
  1. **6 or more café-au-lait patches >1.5 cm in an adult or 6 or more café-au-lait macules >0.5 cm in prepubertal individuals**
  2. **axillary or inguinal freckling**
  3. **2 or more iris hamartomas (Lisch nodules)**
  4. **optic glioma**
  5. **2 or more neurofibromas of any type or one plexiform neurofibroma**
  6. **distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)**
  7. **heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in normal tissue**
- a child of a parent who meets the diagnostic criteria above needs 1 or more to be diagnosed with NF1
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see Pediatrics, P89)

Pathophysiology
- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence of neurofibromin (a tumour suppressor gene)

Epidemiology
- incidence 1 in 3000

Investigations
- Wood's lamp to detect café-au-lait macules in patients with pale skin

Management
- refer to orthopedics, ophthalmology, plastics, and psychiatry
- follow-up annually for brain tumours (e.g. astrocytoma)
- excise suspicious or painful lesions
- see Pediatrics, P89

Oculocutaneous Albinism

Clinical Features
- hypopigmentation of skin and hair, including eyebrows and eyelashes, compared to family members and persons of same ethnicity
- ocular involvement: decreased retinal pigmentation, impaired vision, photophobia, nystagmus, strabismus

Pathophysiology
- group of genetic disorders of melanin biosynthesis
- autosomal recessive

Epidemiology
- 1 in 20000
- varies across ethnic groups

Investigations
- often clinical diagnosis, may consider molecular testing

Management
- sun protection
- close surveillance for skin cancers with whole body skin examinations

Vitiligo

Clinical Features
- primary pigmentary disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply demarcated white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

Pathophysiology
- acquired autoimmune destruction of melanocytes

Interventions for Vitiligo
Cochrane DB Syst Rev 2015;2:CD003263
Purpose: To assess the effects of existing interventions used in the management of vitiligo.
Method: Systematic review of RCTs assessing the effects of vitiligo treatments (topical treatments, light therapies, oral treatments, surgical methods). Primary outcomes were quality of life and >75% re-pigmentation.
Results: Ninety-six RCTs with 4512 participants were deemed eligible, of which only 25 reported on the primary outcomes and were finally included. Re-pigmentation was better with combination therapy (calcipotriol plus PUVA, than PUVA alone; hydrocortisone-17-butyrate plus excimer laser vs. excimer laser alone; oral minipulse of prednisolone (OMP) plus narrowband UVB (NB-UVB) vs. OMP alone; azathioprine with PUVA vs. PUVA alone; 8-methoxypsoralen (8-MOP) plus sunlight vs. psoralen). A non-significant increase in the proportion of participants with >75% re-pigmentation was noted in favour of NB-UVB compared to PUVA. Compared to PUVA, the NV-UVB group reported lower incidences of nausea and erythema, but not itching.
Conclusions: Some studies support existing therapies for vitiligo management, but follow-up is needed to assess the permanence of re-pigmentation and higher quality RCTs need to be conducted.

Epidemiology
- 1 in 100 incidence
- 30 in 100 with positive family history

Investigations
- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison's disease, T1DM
- Wood's lamp to detect lesions: illuminates UV light onto skin to detect amelanosis (porcelain white discolouration)

Management
- sun avoidance and protection
- topical calcineurin inhibitor (e.g. tacrolimus, pimecrolimus) or TCS
- PUVA or NB-UVB
- Topical ruxolitinib (Janus kinase inhibitor) is a newly approved therapy for nonsegmental vitiligo in patients age 12 or older
- camouflage
- "bleaching" normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation

Infections

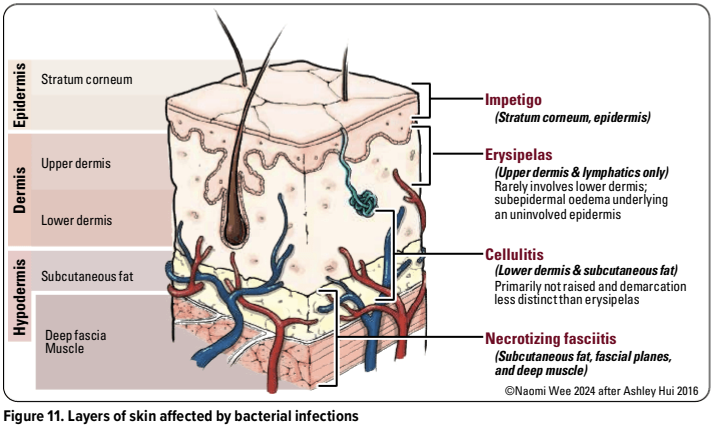

Figure 11. Layers of skin affected by bacterial infections

Bacterial Infections: Epidermis

IMPETIGO

Clinical Features
- acute purulent infection which appears vesicular; progresses to golden yellow "honey-crusted" lesions surrounded by erythema
- can present with bullae
- common sites: face, arms, legs, and buttocks

Etiology
- GAS, *S. aureus*, or both

Epidemiology
- preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

Differential Diagnosis
- infected eczema, HSV, VZV

Investigations
- usually clinical diagnosis
- Gram stain and culture of lesion fluid or biopsy

Management
- remove crusts, use saline compresses, and topical antiseptic soaks bid
- localized: topical antibiotics (e.g. mupirocin 2% or fusidic acid 2% (Canada only) tid; continue for 7-10 d after resolution, or ozenaxacin 1% cream bid for 5 d)
- extensive: systemic antibiotics (e.g. dicloxacillin or cephalexin for 7-10 d)

Staphylococcal Scalded Skin Syndrome
- see Emergency Medicine, ER43

Bacterial Infections: Dermis

Table 17. Comparison of Erysipelas and Cellulitis

	Clinical Features	Etiology	Complications	Differential Diagnosis	Investigations	Management
Erysipelas	Involves upper dermis Confluent, erythematous, sharp raised edge, warm plaque, well demarcated Very painful ("St. Anthony's fire") Sites: face and legs Systemic symptoms: fever, chills, headache, weakness (if present, sign of more serious infection)	GAS	Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy Spreads via lymphatics	DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis	Clinical diagnosis: rarely do skin/blood culture If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology	1st line: penicillin, cephalexin, cloxacillin or cefazolin 2nd line: clindamycin If allergic to penicillin, use erythromycin
Cellulitis	Involves lower dermis/subcutaneous fat Unilateral erythematous flat lesion, often with vesicles, poorly demarcated, not uniformly raised Tender Sites: commonly on legs Systemic symptoms (uncommon): fever, leukocytosis, lymphadenopathy	GAS, *S. aureus* (large sized wounds), Haemophilus influenzae (periorbital), *Pasteurella multocida* (dog/cat bite)	Uncommon	Same as erysipelas	Same as erysipelas	1st line: cloxacillin or cefazolin/cephalexin clindamycin Hospitalized and MRSA positive: vancomycin Children: cefuroxime If DM (foot infections): TMP/SMX and metronidazole

COMMON HAIR FOLLICLE INFECTIONS

Table 18. Comparison of Superficial Folliculitis, Furuncles, and Carbuncles

	Clinical Features	Etiology	Management
Superficial Folliculitis	Superficial infection of the hair follicle (versus pseudofolliculitis: inflammation of follicle due to friction, irritation, or occlusion) Acute lesion consists of a dome-shaped pustule at the mouth of hair follicle Pustule ruptures to form a small crust Sites: primarily scalp, shoulders, anterior chest, upper back, other hair-bearing areas	Normal non-pathogenic bacteria (*Staphylococcus* – most common; Pseudomonas – hot tub) *Pityrosporum*	Antiseptic (Hibiclens®) Topical antibacterial (fusidic acid, mupirocin, erythromycin, or clindamycin) Oral cloxacillin or cephalexin for 7-10 d
Furuncles (Boils)	Red, hot, tender, inflammatory nodules with central yellowish point, which forms over summit and ruptures Involves subcutaneous tissue that arises from a hair follicle Sites: hair-bearing skin (thigh, neck, face, axillae, perineum, buttocks)	*S. aureus*	Incise and drain large furuncles to relieve pressure and pain If afebrile: hot wet packs, topical antibiotic If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&S) Cloxacillin or cephalexin for 1-2 wk (especially for lesions near external auditory canal/nose, with surrounding cellulitis, and not responsive to topical therapy)
Carbuncles	Deep-seated abscess formed by multiple coalescing furuncles Usually in areas of thicker skin Occasionally ulcerates Lesions drain through multiple openings to the surface Systemic symptoms may be associated	*S. aureus*	Same as for furuncles

SKIN ABSCESS

Clinical Features
- painful, fluctuant, erythematous nodule, with or without surrounding cellulitis
- spontaneous drainage or purulent material may be discharged, regional adenopathy may be observed
- may progress to furuncle (deep infection of hair follicle) or carbuncle (collection of furuncles)
- sites: back of the neck, face, axillae, buttocks

Pathophysiology
- one or more pathogens; *S. aureus* with GAS and gram-negative bacilli with anaerobes is common in the perioral, perirectal, or vulvovaginal areas
- collection of pus within the dermis or subcutaneous tissue

Investigations
- clinical diagnosis; laboratory testing with uncomplicated infection in absence of comorbidities or complications is not required

Management
- if drainable abscess, incise and drain
- culture of debrided materials and antibiotics for the following circumstances:
  - severe local infection, systemic signs of infection, history of multiple/recurrent abscesses, presence of underlying comorbidities, immunosuppression, failure of initial antibiotic therapy, extremes of age (i.e. very young or very old), special exposures (e.g. animal bites), prophylaxis against infective endocarditis
- culture of debrided materials is not required in healthy patients who do not receive antibiotics

Bacterial Infections: Epidermis and Dermis

CUTANEOUS ANTHRAX

Clinical Features
- painless, pruritic, red-brown papule with surrounding edema and erythema
- lesions blister and then ulcerate, developing a black eschar
- often associated with systemic symptoms: lymphadenopathy, fever, myalgia, nausea, vomiting

Pathophysiology
- caused by Bacillus anthracis

Investigations
- Gram stain and culture
- polymerase chain reaction (PCR)
- full-thickness punch biopsy

Management
- oral antibiotic: ciprofloxacin, levofloxacin, or doxycycline

LEPROSY
- see Infectious Diseases, ID21

PILONIDAL CYST
- see General and Thoracic Surgery, GS49

Dermatophytoses

Clinical Features
- infection of skin, hair, and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

Pathophysiology
- digestion of keratin by dermatophytes resulting in scaly skin, broken hairs, crumbling nails/onycholysis

Etiology
- *Trichophyton, Microsporum, Epidermophyton* species (*Pityrosporum* is a superficial yeast and not a dermatophyte)

Investigations
- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia

Management
- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type): clotrimazole, ketoconazole, terbinafine, or ciclopirox olamine cream applied bid
- oral therapy is indicated for onychomycosis and tinea capitis: terbinafine (Lamisil® – CYP2D6 inhibitor, liver toxicity) or itraconazole (Sporanox® – CYP3A4 inhibitor, liver toxicity)

A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses
NEJM 2017;376:2545-2555
Purpose: To determine the appropriate management of uncomplicated skin abscesses.
Study: Multi-centre, prospective, double-blind trial involving outpatient adults and children with abscesses 5 cm or smaller, stratified by presence of surgically drainable abscess, abscess size, number of sites of skin infection, and presence of non-purulent cellulitis. Following incision and drainage, participants were randomly assigned to 10 d courses of clindamycin, TMP-SMX or placebo. Primary outcome was clinical cure 7 to 10 d after treatment end. Intention-to-treat analyses were conducted.
Results: Seven hundred and eighty-six participants were enrolled (505 adults, 281 children). 10 d after therapy, the cure rate was similar between clindamycin and TMP-SMX (83.1% vs. 81.7%; P=0.73), and was higher than that of the placebo group (68.9%; P=0.001 for both comparisons). Among those who were cured, new infections at 1 mo follow-up were less common in the clindamycin group than the TMP-SMX or placebo groups (6.8% vs. 11.1%; P=0.03 vs. 12.4%; P=0.06). Adverse events were more frequent with clindamycin than either of the other groups (21.9% vs. 11.1% vs. 12.5%), though all resolved without sequelae.
Conclusions: Clindamycin or TMP-SMX in conjunction with incision and drainage for simple abscesses improves short-term outcomes compared to incision and drainage alone, though side effects must be considered.

Table 19. Different Manifestations of Dermatophyte Infection

	Clinical Features	Differential Diagnosis	Investigations	Management
Tinea Capitis	Round, scaly patches of alopecia, possibly with broken off hairs; pruritic Sites: scalp, eyelashes, and eyebrows; involving hair shafts and follicles Kerion (boggy, elevated, purulent inflamed nodule/plaque) may form secondary to infection by bacteria and result in scarring May have occipital lymphadenopathy Affects children (mainly Black), immunocompromised adults Very contagious and may be transmitted from barber, hats, theatre seats, pets	Alopecia areata, psoriasis, seborrheic dermatitis, trichotillomania	Wood's light examination of hair: green fluorescence only for Microsporum infection Culture of scales/hair shaft Microscopic examination of KOH preparation of scales or hair shafts	Terbinafine (Lamisil®) x 4 wk N.B.: oral agents are required to penetrate the hair root where dermatophyte resides Adjunctive antifungal shampoos or lotions may be helpful, and may prevent spread (e.g. selenium sulfide 2.5%, ketoconazole, ciclopirox)
Tinea Corporis (Ringworm)	Pruritic, scaly, round/oval plaque with active erythematous margin, ± central clearing Sites: trunk, limbs, face	Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis	Microscopic examinations of KOH prep of scales show hyphae Culture of scales	Topicals: clotrimazole 1%, ketoconazole 2%, miconazole 2%, terbinafine, or ciclopirox olamine cream bid for 2-4 wk Oral: terbinafine (Lamisil®), or itraconazole (Sporanox®), or fluconazole, or ketoconazole if extensive
Tinea Cruris ("Jock Itch")	Scaly patch/plaque with a well-defined, curved border and central clearing Pruritic, erythematous, dry/macerated Sites: starts medial thigh, spreads centrifugally to perineum, gluteal cleft, buttocks	Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma		
Tinea Pedis (Athlete's Foot)	Pruritic scaling and/or maceration of the web spaces, and powdery scaling of soles Acute infection: interdigital (especially 4th web space) red/white scales, vesicles, bullae, often with maceration Secondary bacterial infection may occur Chronic: non-pruritic, pink, scaling keratosis on soles, and sides of feet May present as flare-up of chronic tinea pedis Predisposing factors: heat, humidity, occlusive footwear	AD, contact dermatitis, dyshidrotic dermatitis, erythrasma, intertrigo, inverse psoriasis		
Tinea Manuum	Primary fungal infection of the hand is rare; usually associated with tinea pedis Acute: blisters at edge of red areas on hands Chronic: single dry scaly patch	AD, contact dermatitis, granuloma annulare, psoriasis		
Tinea Unguium (Onychomycosis)	Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris Toenail infections usually precede fingernail infections T. rubrum (90% of all toenail infections)	Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophy, bacterial infection	Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae Culture of subungual scraping or nail clippings on Sabouraud's agar Periodic acid-Schiff (PAS) stain of nail clipping by pathology	Terbinafine (Lamisil®) (6 wk for fingernails, 12 wk for toenails) Itraconazole (Sporanox®) 7 d on, 3 wk off (2 pulses for fingernails, 3 pulses for toenails) Topical: ciclopirox (Penlac®); nail lacquer (often ineffective), Efinaconazole (Jublia®) (48 wk)
Tinea Barbae	Superficial inflamed annular lesions; pustules and crusting around hairs Inflammatory kerion may occur and result in scarring hair loss Predominantly affects men who work with animals Site: beard area	Folliculitis, malignant lymphoma, sporotrichosis	Same as for tinea corporis	Terbinafine (Lamisil®) or Itraconazole (Sporanox®) x 4 wk

DIAPER RASH

- see Pediatrics, P15, P45

Parasitic Infections

CUTANEOUS LARVA MIGRANS

Clinical Features

- erythematous pruritic papules at site of initial infection
- larvae migrate under skin causing serpiginous eruption of red pruritic lines
- sites: often feet, legs, buttocks; anywhere skin comes into contact with contaminated sand or soil

Pathophysiology

- parasitic infection caused by hookworm larvae, most commonly from dog or cat feces

Epidemiology

- most common in tropical or subtropical regions

Management

- self-limiting, often resolves without treatment within a few wk
- consider treatment with anthelmintics, antihistamines

CUTANEOUS LEISHMANIASIS

Clinical Features

- begins as a solitary pink painless papule, enlarges to nodule or plaque-like lesion with central ulceration
- incubation time typically 2 wk to 6 mo

Pathophysiology
- transmitted by sandflies infected with Leishmania

Investigations
- histology, culture, and PCR

Management
- most cases resolve spontaneously
- may consider treatment with oral antifungals (e.g. fluconazole, ketoconazole) or parenteral treatment in severe or complicated cases

SCABIES

Clinical Features
- characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- primary lesion: superficial linear burrows; inflammatory papules and nodules in the axilla and groin
- secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- common sites: axillae, groin, buttocks, hands/feet (especially web spaces); sparing of head and neck (except in infants)

Pathophysiology
- primarily transmitted through prolonged direct skin-skin contact, but scabies mites remain alive 2-3 d on clothing/sheets
- incubation of 1 mo, then pruritus begins
- re-infection followed by hypersensitivity in 24 h

Etiology
- Sarcoptes scabiei (a mite)
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

Differential Diagnosis
- atopic/contact dermatitis, arthropod bites, asteatotic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)

Investigations
- microscopic examination of root and content of burrow and mineral oil mount for mites, eggs, feces
- skin biopsy may sometimes show scabies mite

Management
- bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment 7 d after first treatment)
- Ivermectin
- change underwear and linens; wash twice with detergent in hot water cycle, then machine dry
- treat family and close contacts
- pruritus may persist for 2-3 wk after effective treatment due to prolonged hypersensitivity reaction
- mid-potency TCS and antihistamines for symptom management after treatment with permethrin

LICE (PEDICULOSIS)

Clinical Features
- intensely pruritic, red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs; red, excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs; excoriations
- body lice: nits and lice in seams of clothing; excoriations and secondary infection mainly on shoulders, belt-line, and buttocks

Etiology
- *Phthirus pubis* (pubic), *Pediculus humanus capitis* (scalp), *Pediculus humanus humanus* (body): attaches to body hair and feeds on the nearby body site
- can transmit infectious agents (e.g. Bartonella quintana, Rickettsia prowazekii)

Differential Diagnosis
- bacterial infection of scalp, seborrheic dermatitis

Diagnosis
- lice visible on inspection of affected area or clothing seams

Management
- permethrin 1%: Nix® cream rinse (ovicidal), RC & Cor® shampoo, or Kwellada-P® shampoo
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 d after first treatment
- shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle, then machine dry
- children are medically cleared to return to school after first treatment

BED BUGS (HEMIPTERA)

Clinical Features
- burning wheals, turning to firm papules, often in groups of three – "breakfast, lunch, and dinner" – in areas with easy access (face, neck, arms, legs, hands)

Etiology
- caused by *Cimex lectularius*, a small insect that feeds mainly at night (hides in crevices in walls and furniture during the day)

Differential Diagnosis
- dermatitis herpetiformis, drug eruptions, ecthyma, other insect bites, scabies

Investigations
- none required, but lesional biopsy can confirm insect bite reaction

Management
- professional fumigation
- TCS and oral H1-antagonists for symptomatic relief
- definitive treatment is removal of clutter in home and application of insecticides to walls and furniture

Viral Infections

HERPANGINA

Clinical Features
- small vesicles form in mouth after exposure to virus
- lesions evolve into painful shallow oral ulcers, 1-5 mm in size, yellowish with an erythematous base
- often associated with sore throat, dysphagia, and headache

Pathophysiology
- caused by Coxsackie A viruses, highly contagious

Epidemiology
- most common in children and young adults

Investigations
- typically clinical diagnosis

Management
- self-limited
- symptomatic treatment, acetaminophen for fever and pain

HERPES SIMPLEX VIRUS

Clinical Features
- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- primary
  - children and young adults
  - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - followed by antibody formation and latency of virus in dorsal nerve root ganglion
- secondary
  - recurrent form seen in adults; much more common than primary
  - prodrome: tingling, pruritus, pain
  - triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- complications: dendritic corneal ulcer, EM, herpes simplex encephalitis (infants at risk), HSV infection on AD causing Kaposi's varicelliform eruption (eczema herpeticum)

- two biologically and immunologically different subtypes: HSV-1 and HSV-2
  - HSV-1
    - typically "cold sores" (grouped vesicles at the mucocutaneous junction which quickly burst)
    - recurrent on face, lips, and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)
  - HSV-2
    - usually sexually transmitted; incubation 2-20 d
    - gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
    - vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
    - urethritis: watery discharge in males
    - recurrent on vulva, vagina, penis for 5-7 d
    - differential diagnosis of genital ulcers: candidal balanitis, chancroid, syphilitic chancres

Both HSV-1 and HSV-2 can occur on face or genitalia

Investigations

- Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
- viral culture, electron microscopy, PCR, and direct fluorescence antibody test of specimen taken from the unroofed base of a relatively new lesion
- serologic testing for antibody for current or past infection if necessary

Management

- oral herpes
  - treatment may or may not needed depending on length of episode
  - consider treating immunocompromised patients and recurrent/severe episodes with oral antivirals (i.e. acyclovir 400 mg orally 5 times daily for 5 days)
- genital herpes
  - test and treat concurrent STIs, pain control with sitz baths, and analgesia
  - first episode: acyclovir 400mg PO 3x daily for 7-10 days
  - recurrent genital herpes can be treated with daily suppressive therapy (i.e. acyclovir 400 mg PO bid) or episodic therapy (started during prodromal phase or within 1 day of lesion onset, i.e. acyclovir 800 mg orally twice daily for 5 days or 3 times daily for 2 days)
  - famciclovir and valacyclovir may be substituted and have better enteric absorption and less frequent dosing
  - for active lesions in pregnancy (see Obstetrics, OB31)

Erythema Multiforme
Etiology: most often HSV or *Mycoplasma pneumoniae*, rarely drugs
Morphology: macules/papules with central vesicles; classic bull's-eye pattern of concentric light and dark rings (typical target lesions)
Management: symptomatic treatment (oral antihistamines, oral antacids); corticosteroids in severely ill (controversial); prophylactic oral acyclovir for 6-12 mo for HSV-associated EM with frequent recurrences

HERPES ZOSTER VIRUS (SHINGLES)

Clinical Features

- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last d-wk
- pain can be pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Ramsay Hunt syndrome (see Otolaryngology, OT23)
- Hutchinson's sign: shingles on the tip of the nose signifies ocular involvement
  - shingles in this area involves the nasociliary branch of the ophthalmic branch of the trigeminal nerve (V1)
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV

HZV typically involves a single dermatome; and lesions rarely cross the midline

Etiology

- caused by reactivation of VZV
- risk factors: old age, immunosuppression, occasionally associated with hematologic malignancy

Differential Diagnosis

- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)

Investigations

- none required, but can do Tzanck test, direct fluorescence antibody test, or viral culture to rule out HSV

Prevention

- routine vaccination in >50 yr with Shingrix® (recombinant zoster vaccine) preferred (can also use in >60 yr Zostavax® (live zoster vaccine))

Management

- compress with normal saline, Burow's or betadine solution
- oral antivirals: famciclovir, valacyclovir, or acyclovir for 7 d; must initiate within 72 h to be of benefit
- analgesia: NSAIDs, acetaminophen for mild-moderate pain; opioids if severe
- post-herpetic neuralgia: tricyclic antidepressants, anticonvulsants (gabapentin, pregabalin)

MOLLUSCUM CONTAGIOSUM

Clinical Features
- discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus (Molluscum contagiosum virus)
- common sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

Etiology
- virus is spread via direct contact, auto-inoculation, sexual contact
- common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)
- virus is self-limited but can take 1-2 yr to resolve

Investigations
- none required, however can biopsy to confirm diagnosis

Management
- topical cantharidin
- cryotherapy
- curettage
- topical retinoids
- Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

WARTS (HUMAN PAPILLOMAVIRUS INFECTIONS)

Table 20. Different Manifestations of HPV Infection

	Definition and Clinical Features	Differential Diagnosis	Distribution	HPV Type
Verruca Vulgaris (Common Warts)	Hyperkeratotic, elevated, discrete epithelial growths with papillated surface caused by HPV Paring of surface reveals punctate, red-brown specks (thrombosed capillaries)	Molluscum contagiosum, seborrheic keratosis	Located at trauma sites: fingers, hands, knees of children and teens	At least 80 types are known
Verruca Plantaris (Plantar Warts) **Verruca Palmaris** (Palmar Warts)	Hyperkeratotic, shiny, sharply marginated growths Paring of surface reveals red-brown specks (capillaries), interruption of epidermal ridges	May need to scrape ("pare") lesions to differentiate wart from callus and corn	Located at pressure sites: metatarsal heads, heels, toes	Commonly HPV 1, 2, 4, 10
Verruca Planae (Flat Warts)	Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration Common in children	Syringoma, seborrheic keratosis, molluscum contagiosum, lichen planus	Sites: face, dorsa of hands, shins, knees	Commonly HPV 3, 10
Condyloma Acuminata (Genital Warts)	Skin-coloured pinhead papules to soft cauliflower-like masses in clusters Can be asymptomatic, lasting mo to yr Highly contagious, transmitted sexually and non-sexually (e.g. Koebner phenomenon via scratching, shaving), and can spread without clinically apparent lesions Investigations: acetowhitening (subclinical lesions seen with acetic acid 5% x5 min and hand lens) Complications: fairy-ring warts (satellite warts at periphery of treated area of original warts)	Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), molluscum contagiosum	Sites: genitalia and perianal areas	Commonly HPV 6 and 11 HPV 16, 18, 31, 33 cause cervical dysplasia, SCC, and invasive cancer

Treatment for Warts
- first line therapies
  - salicylic acid preparations (patches, solutions, creams, ointments), cryotherapy
- second line therapies
  - topical imiquimod, topical 5-fluorouracil, topical tretinoin, podophyllotoxin
- third line therapies
  - curettage, cautery, surgery for non plantar warts, CO2 laser, oral cimetidine (particularly children), intralesional bleomycin (plantar warts), trichloroacetic acid, diphencyprone

CHICKEN POX (VARICELLA)
- see Pediatrics, P63

ERYTHEMA INFECTIOSUM (FIFTH DISEASE)
- see Pediatrics, P62

HAND-FOOT-AND-MOUTH DISEASE
- see Pediatrics, P62

MEASLES
- see Pediatrics, P62

PARVOVIRUS
- see Pediatrics, P62

ROSEOLA
- see Pediatrics, P62

RUBELLA
- see Pediatrics, P63

VERRUCAE VULGARISMS
- see *Table 20, D36*

Yeast Infections

CANDIDIASIS

Etiology
- many species of Candida (70-80% of infections are from *Candida albicans*)
- opportunistic infection in those with predisposing factors (e.g. trauma, malnutrition, immunodeficiency)

Candidal Paronychia
- clinical features: painful red swelling of periungual skin
- management: topical agents not as effective; oral antifungals recommended

Candidal Intertrigo
- clinical features
  - macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
  - peripheral "satellite" pustules
  - starts as non-infectious maceration from heat, moisture, and friction
- predisposing factors: obesity, DM, systemic antibiotics, immunosuppression, malignancy
- management: keep area dry, terbinafine, ciclopirox olamine, ketoconazole/clotrimazole cream bid until rash clears

Oral terbinafine (Lamisil®) is not effective because it is not secreted by sweat glands

PITYRIASIS (TINEA) VERSICOLOR

Clinical Features
- asymptomatic superficial fungal infection with brown/white scaling macules
- affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
- common sites: upper chest and back

Pathophysiology
- microbe produces azelaic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
- affinity for sebaceous glands; requires fatty acids to survive

Etiology
- caused by *Malassezia* sp. (formerly known as *Pityrosporum*)
- also associated with folliculitis and seborrheic dermatitis
- predisposing factors: summer, tropical climates, excessive sweating, Cushing's syndrome, prolonged corticosteroid use

Investigations
- clinical diagnosis but can perform microscopic examination, KOH prep of scales for hyphae and spores

Management
- ketoconazole 2% shampoo or cream daily for 3 d
- selenium sulfide 2.5% lotion applied for 10 min for 7 d
- ciclopirox olamine bid
- systemic fluconazole or itraconazole for 7 d if extensive

Sexually Transmitted Infections

SYPHILIS

Clinical Features
- characterized initially by a painless ulcer (chancre)
- following inoculation, systemic infection with secondary and tertiary stages

Etiology
- Treponema pallidum
- transmitted sexually, congenitally, or rarely by transfusion

Table 21. Stages of Syphilis

	Clinical Features	Investigations	Management
Primary Syphilis	Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-6 wk; chancre may also develop on lips or anus Regional non-tender lymphadenopathy appears <1 wk after onset of chancre DDx: chancroid (painful), HSV (multiple lesions)	CANNOT be based on clinical features alone VDRL negative – repeat weekly for 1 mo FTA-ABS test has greater sensitivity and may detect disease earlier in course Dark field examination – spirochete in chancre fluid or lymph node	Penicillin G, 2.4 million units IM, single dose
Secondary Syphilis	Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre) Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia Lesions heal in 1-5 wk and may recur for 1 yr 3 types of lesions: 1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus) 2. Condyloma lata: wart-like moist papules around genital/perianal region 3. Mucous patches: macerated patches mainly found in oral mucosa	VDRL positive FTA-ABS +ve; –ve after 1 yr following appearance of chancre Dark field +ve in all secondary	Same as for primary syphilis
Tertiary Syphilis	Extremely rare 3-7 yr after secondary Main skin lesion: 'Gumma' – a granulomatous non-tender nodule	As in primary syphilis, VDRL can be falsely negative	Penicillin G, 2.4 million units IM weekly x 3 wk

GONOCOCCEMIA

Clinical Features
- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- common sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis, and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

Etiology
- Neisseria gonorrhoeae

Investigations
- requires high index of clinical suspicion because tests are often negative
- bacterial culture of blood, joint fluid, and skin lesions
- joint fluid cell count and Gram stain

Management
- notify public health authorities
- screen for other STIs
- ceftriaxone 1 g IM or IV every 24 h

Herpes Simplex Virus
- see *Viral Infections, D34*

Human Papillomavirus
- see *Viral Infections, D36*

Pre-Malignant Skin Conditions

Actinic Keratoses (Solar Keratoses)

Clinical Features
- ill-defined, scaly, erythematous papules or plaques associated with sun-damaged skin (solar heliosis)
- initial lesion is a rough erythematous papule with white to yellow scale
- often easier to appreciate on palpation rather than inspection with a gritty, sandpaper-like texture
- sites: areas of sun exposure (face, helices of the ears primarily in men, hairless scalp, neck, upper trunk, dorsal aspects of the hands and forearms)

Pathophysiology
- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of AK to SCC (<1/1000 per yr), but higher likelihood if AK is persistent
- UV-induced p53 gene mutation
- risk factors: increased age, light skin/eyes/hair, immunosuppression, genetic syndromes such as albinism or xeroderma pigmentosum
- risk factors for malignant transformation of AK to SCC: immunosuppression, history of skin cancer, persistence of AK

Types of AK

Erythematous: typical AK lesion

Hypertrophic: thicker, rough papule/plaque

Cutaneous horn: firm hyperkeratotic outgrowth

Actinic cheilitis: confluent AKs on the lip

Pigmented: flat, tan-brown, scaly plaque

Spreading pigmented

Proliferative

Conjunctival: pinguecula, pterygium

Epidemiology
- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III, rare in deeper skin tones as melanin is protective

Differential Diagnosis
- SCC in situ, superficial BCC, seborrheic keratosis

Investigations
- biopsy refractory or suspicious lesions (infiltrative, tender, bleeding spontaneously)

Management
- destructive: shave excision and curettage with electrodesiccation, or cryotherapy
- topical pharmacotherapy (mechanism: destruction of rapidly growing cells or immune system modulation)
  - topical 5-fluorouracil cream (for 2-4 wk), imiquimod 5% (2x/wk for 16 wk), imiquimod 3.75% (daily for 2 wk, and then daily again for 2 wk more)
- photodynamic therapy
- chemical peels (e.g. TCA, phenol)
- excision
- laser resurfacing

Leukoplakia

Clinical Features
- a morphologic term describing homogeneous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

Pathophysiology
- precancerous or pre-malignant condition
- oral variant is strongly associated with tobacco use and alcohol consumption

Epidemiology
- 1-5% prevalence in adult population >30 y/o; peak at age >50
- M>F, fair-skinned
- most common oral mucosal pre-malignant lesion

Differential Diagnosis
- DLE, invasive SCC, candidiasis, lichen planus, oral hairy leukoplakia, white sponge nevus

Investigations
- biopsy due to risk of malignancy

Management
- low-risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, smoking cessation, follow-up
- moderate/dysplastic lesions: excision, cryotherapy
- primary aim of treatment is to decrease the risk of oral SCC

Malignant Skin Tumours

Nonmelanoma Skin Cancers

BASAL CELL CARCINOMA

Subtypes
- nodular BCC (most common)
  - skin-coloured papule/nodule with rolled, translucent ("pearly") telangiectatic border, and depressed/eroded/ulcerated centre
- pigmented BCC
  - areas of pigment in translucent lesion with surface telangiectasia
  - may mimic MM
- superficial BCC
  - thin, tan to red-brown plaque, often with scaly, pearly border, and fine telangiectasia at margin
  - least aggressive subtype
- morpheaform or sclerosing BCC
  - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders, indurated

Pathophysiology
- malignant proliferation of basal keratinocytes of the epidermis
  - low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
  - usually due to UVB light exposure, therefore >80% on sun exposed sites
  - typical latency period of 20-50 yr between time of UV damage and onset of BCC
  - also associated with previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin Syndrome)

Epidemiology
- most common malignancy in humans
- 75% of all malignant skin tumours in >40 y/o, increased prevalence in the elderly
- risk factors: M>F, skin phototypes I and II, chronic cumulative sun exposure, ionizing radiation, immunosuppression, arsenic exposure

Differential Diagnosis
- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular MM, SCC, merkel cell carcinoma (MCC)

Management
- see *Table 22, Management of Nonmelanoma Skin Cancers*
- follow-up for new primary disease or recurrence
- 95% cure rate if lesion <2 cm in diameter or if treated early

Workup/Investigations of Basal Cell Carcinoma and Other Nonmelanoma Skin Cancers
History: duration, growth rate, family/personal history of skin cancer, history of immunosuppression, history of sun exposure, medications, prior therapy to the lesion
Physical: location, size, whether circumscribed, tethering to deep structures, full skin exam, lymph node exam
Biopsy: if shallow lesion, can do shave biopsy; otherwise punch or excisional biopsy may be more appropriate

Surgical Margins
Smaller lesions: electrodessication and curettage with 2-3 mm margin of normal skin
Deep infiltrative lesions: surgical excision with 3-5 mm margins beyond visible and palpable tumour border, which may require skin graft or flap; or Mohs surgery, which conserves tissue and does not require margin control

Table 22. Management of Nonmelanoma Skin Cancers

Treatment Category	Treatment Options	Indications	Disadvantages
Topical	Imiquimod 5% cream (Aldara®)	Superficial BCCs, Bowen's Disease	Side effects: erythema, edema, ulceration, and, scaling
	Cryotherapy	Superficial BCCs, Bowen's Disease Advantages: minimal equipment, simple to perform, cost-effective, no restriction of activity after surgery	Margin around cancer may not be free, potential for scarring, minimally painful, no skin tissue for diagnosis
	5-fluorouracil (Efudex®)	Superficial BCCs, Bowen's Disease	Side effects: pain, burning, swelling
Procedural	Photodynamic therapy	Superficial BCCs Advantages: low cost, tolerable side effect profile	Side effects: pain
	Radiation therapy	Advanced cases of BCC, SCC Advantages: if lesions are located in cosmetically sensitive area	Side effects: alopecia, pigmentary changes, fibrosis, atrophy, buccal mucositis, gingivitis, telangiectasias
Surgical	Shave excision and electrodessication and curettage	Most types of BCCs, Bowen's Disease Advantages: minimal equipment needed, simple to perform, cost-effective, no restriction of activity after surgery	Not used for morpheaform BCC, margin around cancer may not be free, slow healing, possible scarring
	Mohs surgery	BCC and SCC lesions on the face or in areas that are difficult to reconstruct. Can be considered for lentigo maligna and/or melanoma in-situ. Advantages: highest cure rate, good cosmetic results, healthy skin tissue is preserved	Expensive, highly technical, resource intensive, activity restriction after surgery if skin graft/flap needed
	Traditional surgical excision	SCC Advantages: margin around cancer more likely to be free than shave excision, tissue is available for diagnosis, cosmetic satisfaction	Activity restriction after surgery if skin graft/flap needed, healthy tissue around cancer must be removed
Medical Therapy	Vismodegib	Metastatic BCC, Gorlin Syndrome (multiple BCCs)	Side effects: muscle spasms, hair loss, abnormal taste, weight loss, nausea, amenorrhea
	Cemiplimab	Metastatic SCC, metastatic BCC refractory to vismodegib	Side effects: musculoskeletal pain, fatigue, nausea

BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

Clinical Features
- sharply demarcated erythematous patch/thin plaque with scale and/or crusting
- often 1-3 cm in diameter and found on the skin and mucous membranes
- evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

Management
- see *Table 22, Management of Nonmelanoma Skin Cancers, D40*

SQUAMOUS CELL CARCINOMA

Clinical Features
- hyperkeratotic indurated, pink/red/skin-coloured papule/plaque/nodule with surface scale/crust ± ulceration
- more rapid enlargement than BCC
- exophytic (grows outward), may present as a cutaneous horn
- common sites: face, ears, scalp, forearms, dorsum of hands

Pathophysiology
- malignant neoplasm of keratinocytes (primarily vertical growth)
- predisposing factors include: cumulative UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar, and nitrogen mustards), HPV 16 or 18, immunosuppression
- may occur in previous scar (SCC more commonly than BCC)

Epidemiology
- second most common type of cutaneous neoplasm in less pigmented skin types
- most common cutaneous neoplasm in patients with Type 6 skin, typically in non-photoexposed sites (risk factors include chronic wounds or chronically inflamed areas such as discoid lupus, or hidradenitis suppurativa)
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- SCC is the most common cutaneous malignancy in immunocompromised patients such as in organ transplant recipients, with increased mortality as compared to non-immunocompromised population

Differential Diagnosis
- benign: wart, psoriasis, irritated seborrheic keratosis
- pre-malignant: AK, Bowenoid papulosis
- malignant: keratoacanthoma, Bowen's disease, BCC, amelanotic melanoma

Management
- see *Table 22, Management of Nonmelanoma Skin Cancers, D40*
- may require lifelong follow-up (more aggressive treatment than BCC)

Prognosis
- good prognostic factors: early treatment, negative margins, and small size of lesion
- rate of metastasis from primary SCC is 2-5%
- higher risk of metastasis if diameter >2 cm, depth >2 mm, recurrent, involvement of bone/muscle/nerve, location on scalp/ears/nose/lips, immunosuppressed, caused by arsenic ingestion, or tumour arose from scar/chronic ulcer/burn/genital tract/sinus tract

KERATOACANTHOMA

Clinical Features
- rapidly growing, firm, dome-shaped, erythematous or skin-coloured volcano-like nodule with central keratin-filled crater
- may spontaneously regress
- sites: sun-exposed skin

Pathophysiology
- epithelial neoplasm with atypical keratinocytes in epidermis
- low grade variant of SCC

Etiology
- HPV, UV radiation, chemical carcinogens (tar, mineral oil)

Epidemiology
- most common in >50 y/o, rare in <20 y/o

Differential Diagnosis
- treat as SCC until proven otherwise
- nodular BCC, MCC, hypertrophic solar keratosis, verruca vulgaris

Interventions for AK
Cochrane DB Syst Rev 2012;2:CD004415
Purpose: To assess the efficacy of treatments for AK.
Methods: Systematic review of RCTs.
Results: A total of 83 RCTs (10036 patients) were included, evaluating 24 treatments. Cryotherapy, diclofenac, 5-fluorouracil, imiquimod, ingenol mebutate, photodynamic therapy, resurfacing and trichloroacetic acid peel were all effective at treating AK and generally comparable with one another. Skin irritation was more common with diclofenac and 5-fluorouracil. Photodynamic therapy and imiquimod treatment resulted in better cosmetic appearance.
Conclusion: For individual lesions, photodynamic therapy is more effective than cryotherapy. For field-directed treatments, 5-fluorouracil, diclofenac, imiquimod, and ingenol mebutate had comparable efficacy.

Management
- surgical excision or saucerization (shave biopsy) followed by electrodesiccation of the base, treated similarly to SCC
- intralesional methotrexate or 5-fluorouracil injection

Malignant Melanoma

Clinical Features
- malignant characteristics of a mole: "ABCDE" mnemonic
- sites: skin, mucous membranes, eyes, CNS
- ~2/3 arise *de novo* without an associated nevus
- abnormal dermoscopic features

Does this Patient have a Mole or Melanoma?

ABCDE checklist
Asymmetry
Border (irregular and/or indistinct)
Colour (varied)
Diameter (increasing or >6 mm)
Enlargement, elevation, evolution (i.e. change in colour, size, or shape)
Sensitivity 92% (CI 82-96%)
Specificity 100% (CI 54-100%)
JAMA 1998;279:696-701

Clinical Subtypes of Malignant Melanoma
Listed from most to least common subtype
- **superficial spreading melanoma** (60-70% of all melanomas)
- atypical melanocytes initially spread laterally in epidermis, then invade the dermis
- irregular, indurated, enlarging plaques with red/white/blue discolouration, focal papules or nodules
- ulcerate and bleed with growth
- subtype most likely associated with pre-existing nevus
- **nodular melanoma** (15-30% of all melanomas)
- atypical melanocytes that initially grow vertically with little lateral spread
- uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
- rapidly fatal
- may be pink or have no colour at all, this is called an amelanotic melanoma
- EFG = elevated, firm, growing
- **lentigo maligna**
  - MM *in situ* (normal and malignant melanocytes confined to the epidermis)
  - greater than 6 mm (up to several cm) in diameter, tan/brown/black uniformly flat macule or patch with irregular borders
  - lesion grows radially and produces complex colours
  - often seen in the elderly
  - 10% evolve to lentigo maligna melanoma
- **lentigo maligna melanoma (5-15% of all melanomas)**
  - older individuals, ~7th decade
  - malignant melanocytes invading into the dermis
  - associated with pre-existing solar lentigo, not pre-existing nevi
  - flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  - with time, colour changes from uniform brown to dark brown with black and blue
  - found on all skin surfaces, especially those often exposed to sun, such as the face and hands
- **acral lentiginous melanoma (5-10% of all melanomas)**
  - ill-defined dark brown, blue-black macule
  - palmar, plantar, subungual skin
  - melanomas on mucous membranes have poor prognosis
  - most common subtype found in patients with Type 6 skin
- **amelanotic melanoma (2-8% of all melanomas)**
  - little to no pigment
  - pink or red macules, papules, or nodules, some may present with light-brown pigmentation
  - delay in diagnosis may contribute to its poor prognosis
  - MM in young children is more commonly amelanotic variant

Risk Factors for Melanoma

no SPF is a SIN
Sun exposure
Pigment traits (blue eyes, fair/red hair, pale complexion)
Freckling
Skin reaction to sunlight (increased incidence of sunburn)
Immunosuppressive states (e.g. renal transplantation)
Nevi (dysplastic nevi; increased number of benign melanocytic nevi)

Node Dissection for Lesions

Offered to patients with stage IB or higher melanoma (>1 mm Breslow thickness OR 0.8-1 mm with or without ulceration OR <0.8 mm with ulceration)

May be considered in select patients with stage IA melanoma (<0.8 mm without ulceration with presence of risk factors such as age <40, >1 mitoses/mm², lymphovascular invasion, positive deep biopsy margin)

Assess sentinel node at time of wide excision

Pathophysiology
- malignant neoplasm of pigment-forming cells (melanocytes and nevus cells)

Epidemiology
- 1 in 75 (Canada), 1 in 50 (US)
- risk factors: increasing age, fair skin, red hair, positive personal/family history, familial dysplastic nevus syndrome, large congenital nevi (>20 cm), any dysplastic nevi, >50 common nevi, immunosuppression, sun exposure with sunburns, tanning beds
- most common sites: back (M), calves (F)
- worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

Differential Diagnosis
- benign: nevi, solar lentigo, seborrheic keratosis, dermatofibroma, spitz nevus
- malignant: pigmented BCC, dermatofibrosarcoma protuberans

See Landmark Dermatology Trials table for more information on the trial by Hodi et al. 2010, which details improved survival with Ipilimumab in patients with metastatic melanoma.

Management
- excisional biopsy preferable (margin determined by Breslow depth), otherwise incisional biopsy, sentinel lymph node dissection controversial
- remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
- beware of lesions that regress – tumour is usually deeper than anticipated
- anti-CTLA-4 agents (e.g. ipilimumab), anti-PD1 agents (e.g. nivolumab, pembrolizumab), high-dose IFN, chemotherapy (e.g. dacarbazine) as options for unresectable stage II, stage III, and metastatic melanoma. These therapies can also be used as adjuvant therapy in resectable stage II, stage III disease

See Landmark Dermatology Trials table for more information on the BRIM-3 trial comparing the efficacy of BRAF kinase inhibitor vemurafenib (PLX4032) to dacarbazine in patients with metastatic melanoma.

- targeted small molecule BRAF inhibitors such as vemurafenib are an option in patients with BRAF V600E mutations and unresectable or metastatic melanoma
- radiotherapy may be used as adjunctive treatment

Table 23. American Joint Committee on Cancer Staging System Based on Breslow's Thickness of Invasion

Tumour Depth	Stage	Approximate 5-Yr Survival
T1 <1.0 mm	Stage I T1a – T2a	5-yr survival 90%
T2 1.01-2.0 mm	Stage II T2b – T4b	5-yr survival 70%
T3 2.01-4.0 mm	Stage III any nodes	5-yr survival 45%
T4 >4.0 mm	Stage IV any mets	5-yr survival 10%

a = no ulceration; b = ulceration

Other Cutaneous Cancers

CUTANEOUS T-CELL LYMPHOMA

Clinical Features
- Mycosis fungoides (limited superficial type)
  - characterized by slightly atrophic scaling, erythematous patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation, hypopigmentation)
  - common sites include: trunk, buttocks, proximal limbs
  - mildly symptomatic, usually excellent prognosis for early disease
  - hypopigmented subtype most commonly seen in children with deeper skin tones
- Sézary syndrome (widespread systemic type)
  - rare variant characterized by erythroderma, lymphadenopathy, WBC >20 x 109/L with Sézary cells
  - can be considered to have evolved from mycosis fungoides (not initially meeting diagnostic criteria), but more commonly arises de novo
  - associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
  - high mortality

Pathophysiology
- clonal proliferation of skin-homing CD4 T-cells

Epidemiology
- seen in >50 yr, M:F ratio is 2:1

Differential Diagnosis
- tinea corporis, atopic dermatitis, nummular dermatitis, psoriasis, DLE, Bowen's disease, adult T-Cell leukemia-lymphoma (ATL)

Investigations
- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
- blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is characteristic but not diagnostic of Sézary)
- imaging (for systemic involvement)

Management
- Mycosis fungoides
  - depends on stage of disease
  - early stage: TCS, topical chemotherapy, topical retinoids, topical imiquimod, local radiation, and/or PUVA, NB-UVB (311-313 mm)
  - advanced stage: biologics such as brentuximab, low-dose methotrexate, systemic retinoids, PUVA
- Sézary syndrome
  - oral retinoids and IFN
  - extra-corporeal photopheresis
  - may need radiotherapy for total skin electron beam radiation
  - may maintain on UV therapy
  - other chemotherapy agents

KAPOSI SARCOMA

Definition
- an angioproliferative neoplasm that requires infection with human herpesvirus 8 (HHV-8)
- 4 types based on the clinical circumstance at which it develops
  - classical: develops in middle or old age in individuals of Mediterranean descent
  - endemic: seen in sub-Saharan indigenous Africans
  - iatrogenic: associated with immunosuppressive drug therapy and renal allograft recipients
  - AIDS associated

Clinical Features
- purplish, reddish blue, or dark brown/black macules, plaques, and nodules on the skin
- skin nodules can range in size from very small to several centimeters in diameter, and lesions may ulcerate and bleed
- lesions typically present on the distal extremities
- also affects the gastrointestinal tract and lymphatics leading to secondary lymphoedema

Epidemiology
- incidence is 0.02% to 0.06% of all malignant tumours, M>F

Differential Diagnosis
- well-differentiated angiosarcoma, benign lymphangiomatosis, hypertrophic lichen planus

Investigations
- biopsy
- PCR - can identify HHV-8 DNA sequences

Treatment
- surgery, cryotherapy, laser surgery, photodynamic therapy, topical retinoids, immunomodulators for superficial macules and plaques
- radiation therapy, systemic chemotherapy

Diseases of Hair Density

Hair Growth

- hair grows in a cyclic pattern that is defined in 3 stages (most scalp hairs are in anagen phase)
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and dihydrotestosterone (DHT); this response is genetically controlled

Hair Regrowth Potential
Ability to regrow hair depends on location of inflammatory infiltrates on hair follicle as stem cells are located at the upper part (bulge region) of the hair follicle
- **Scarring alopecia**: Inflammatory infiltrates found in upper part of hair follicles, destroying stem cells
- **Non-scarring alopecia:** Hair follicle is not permanently damaged, and therefore spontaneous or treatment-induced regrowth is possible

Non-Scarring (Non-Cicatricial) Alopecia

ANDROGENETIC ALOPECIA

Clinical Features
- male- or female-pattern alopecia
- males: fronto-temporal areas progressing to vertex, entire scalp may be bald
- females: widening of central part, "Christmas tree" pattern

Pathophysiology
- action of DHT on hair follicles

Epidemiology
- males: early 20s-30s
- females: 40s-50s

Management
- camouflage techniques (i.e. wigs, hair extensions, powders, concealing lotions or sprays)
- topical minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
- females: spironolactone (anti-androgenic effects), cyproterone acetate (Diane-35®)
- males: finasteride (Propecia®) (5-α-reductase inhibitor) 1 mg/d
- oral minoxidil
- procedural (hair transplant, platelet-rich plasma)

DDx of Non-Scarring (Non-Cicatricial) Alopecia

Autoimmune
- Alopecia areata

Endocrine
- Hypothyroidism
- Androgens

Micronutrient deficiencies
- Iron
- Zinc

Toxins
- Heavy metals
- Anticoagulants
- Chemotherapy
- Vitamin A

Trauma to the hair follicle
- Trichotillomania
- Traction /Tight ponytail or braiding styles

Other
- Syphilis
- Severe illness
- Childbirth

TELOGEN EFFLUVIUM

Clinical Features
- uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle

Pathophysiology
- variety of precipitating factors (i.e. post-partum, psychological stress, major illness)
- hair loss typically occurs 2-4 mo after exposure to precipitant
- regrowth occurs within a few mo but may not be complete

Precipitants of Telogen Effluvium

"SEND" hair follicles out of anagen and into telogen
Stress (biological and psychological) and **S**calp disease (surgery)
Endocrine (hypothyroidism, post-partum)
Nutritional (iron and protein deficiency)
Drugs (acitretin, heparin, lithium, IFN, β-blockers, valproic acid, SSRIs)

ANAGEN EFFLUVIUM

Clinical Features
- hair loss due to insult of hair follicle impairing its mitotic activity (growth stage)

Pathophysiology
- precipitated by chemotherapeutic agents (most common), other medications (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
- dose-dependent effect
- hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
- reversible effect; follicles resume normal mitotic activity few wk after agent stopped

ALOPECIA AREATA

Clinical Features
- autoimmune disorder characterized by patches of complete hair loss often localized to scalp, but can affect eyebrows, beard, eyelashes, etc.
- may be associated with dystrophic nail changes – fine stippling, pitting
- "exclamation mark" pattern (hairs fractured and have tapered shafts, i.e. looks like "!")
- may be associated with autoimmune conditions: pernicious anemia, vitiligo, thyroid disease, Addison's disease
- spontaneous regrowth may occur within mo of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress
- alopecia totalis: complete loss of hair on scalp
- alopecia universalis: complete loss of scalp hair, eyelashes, eyebrows, and body hair

Management
- excellent prognosis for localized disease
- TCS and intralesional steroids (triamcinolone acetonide) can be used for isolated patches
- topical immunotherapy (diphencyprone, anthralin)
- systemic immunosuppressants for refractory or extensive disease
- immunomodulatory (diphencyprone, anthralin)
- newer treatments: janus kinase inhibitors

OTHER
- trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
- traumatic (e.g. tight braiding styles, wearing tight ponytails, tight tying of hair coverings)

Scarring (Cicatricial) Alopecia

Clinical Features
- irreversible loss of hair follicles with fibrosis

Etiology
- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (HSV)
- primary inflammatory – subdivided into lymphocytic, neutrophilic, and mixed
  - lymphocytic:
    - lichen planus (lichen planopilaris) – white scale around hair follicles, up to 50% have lichen planus at other body sites
    - DLE (note that SLE can cause an alopecia unrelated to DLE lesions which are non-scarring)
    - central centrifugal cicatricial alopecia (CCCA): seen in up to 40% of Black women, starting at central scalp; one of the most commonly diagnosed scarring alopecias, may be associated with hair care practices
    - keratosis follicularis spinulosa decalvans (autosomal dominant, X-linked)
  - neutrophilic:
    - folliculitis decalvans – discharge of pus and blood, tufting of hair follicles
    - dissecting cellulitis of the scalp – follicular papules, pustules, nodules, and abscesses develop on the scalp
  - mixed
    - acne keloidalis nuchae – dome-shaped papules, pustules, and plaques on the occipital scalp
- morphea: "coup de sabre" with involvement of centre of scalp

Investigations
- biopsy from active border

Management
- infections: treat underlying infection
- inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials, immunosuppressants (e.g. cyclosporine)

Hair Loss

TOP HAT
Telogen effluvium, Tinea capitis
Out of iron, zinc
Physical: trichotillomania, tight ponytail or braiding styles
Hormonal: hypothyroidism, androgenic
Autoimmune: SLE, alopecia areata
Toxins: heavy metals, anticoagulants, chemotherapy, vitamin A, SSRIs

Non-scarring alopecia: intact hair follicles on exam → biopsy not required (but may be helpful)
Scarring alopecia: absent hair follicles on exam → biopsy required

Alopecia Areata Subtypes
Alopecia totalis: loss of all scalp hair and eyebrows
Alopecia universalis: loss of all body hair

Postmenopausal Hair Changes
- estrogen regulates the growth and cycling of hair follicles
- hormonal changes (e.g. reduced estrogen) during menopause leads to decreased hair diameter, growth rate, and percentage of hairs in the anagen phase; moreover, chronological age affects hair density
- these compounded effects of the two factors above (hormone changes and aging) may lead to a perception of decreased scalp hairs in middle-aged women

Hypertrichosis

Clinical Features
- excessive hair growth that is an outlier for age, sex, or race
- is not associated with androgen sensitive areas
- can be localized/circumscribed, or generalized, acquired or congenital

Etiology
- congenital causes of hypertrichosis:
  - localized: congenital circumscribed hypertrichosis: congenital melanocytic nevus , congenital Becker nevus, smooth muscle hamartoma, underlying neurofibroma
  - generalized: congenital hypertrichosis lanuginosa, congenital generalized hypertrichosis, Brachmann-de-Lange syndrome, teratogen exposure
- acquired causes of hypertrichosis:
  - localized: acquired Becker nevus, chemicals (i.e. iodine, minoxidil, psoralens, TCS), orthopedic casts/splits, fracture, friction (i.e. scratching in lichen simplex) , trichomegaly (long eyelashes that can arise from local latanoprost treatment)
  - generalized: cerebral disturbances, acrodynia, infection, malnutrition, dermatomyositis, thyroid abnormalities

Management
- acquired: treat the underlying cause
- congenital: hair removal (i.e. shaving, waxing, laser hair removal), makeup, lighten hair with commercial bleach or 6% hydrogen peroxide

HIRSUTISM
- see Gynecology, GY25

Nails and Disorders of the Nail Apparatus

Table 24. Nail Changes in Systemic and Dermatological Conditions

Nail Abnormality	Definition/Etiology	Associated Disease
NAIL PLATE CHANGES		
Clubbing	Proximal nail plate has greater than 180° angle to nail fold, watch-glass nails, bulbous digits	Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.
Koilonychia	Spoon shaped nails	Iron deficiency, malnutrition, DM
Onycholysis	Separation of nail plate from nail bed	Psoriasis, dermatophytes, thyroid disease, repetitive trauma
Onychogryphosis	Hypertrophy of the nail plate producing a curved, claw-like deformity	Poor circulation, chronic inflammation, tinea
Onychohemia	Subungual hematoma	Trauma to nail bed
Onychomycosis	Fungal infection of nail (e.g. dermatophyte, yeast, mould)	HIV, DM, peripheral arterial disease
Onychomadesis	Nail plate detachment from proximal nail fold due to severe trauma that produces a complete arrest of nail matrix activity	Manicures, eczema, chronic paronychia, severe or febrile illness, erythroderma
SURFACE CHANGES		
V-Shaped Nicking	Distal margin has v-shaped loss of the nail plate	Darier's disease (keratosis follicularis)
Pterygium Inversum Unguis	Distal nail plate does not separate from underlying nail bed	Scleroderma
Pitting	Punctate depressions that migrate distally with growth	Psoriasis (random pattern), alopecia areata (geometric, grid-shaped arrangement), eczema
Transverse Ridging	Transverse depressions, often more in central portion of nail plate	Serious acute illness slows nail growth (when present in all nails = Beau's lines), eczema, chronic paronychia, trauma
Transverse White Lines	Bands of white discolouration	Poisons, hypoalbuminemia (Muehrcke's lines)
Onychorrhexis	Brittle nails leading to longitudinal ridging	Lichen planus, psoriasis, normal aging, fungal infection

Table 24. Nail Changes in Systemic and Dermatological Conditions

Nail Abnormality	Definition/Etiology	Associated Disease
COLOUR CHANGES		
Yellow		Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis, tobacco use
Green		Pseudomonas
Black		Melanoma, hematoma
Brown		Nicotine use, psoriasis, poisons, longitudinal melanonychia (more common in Fitzpatrick V and VI)
Splinter Hemorrhages	Extravasation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows	Trauma, bacterial endocarditis, blood dyscrasias, psoriasis
Oil Spots	Brown-yellow discolouration	Psoriasis
Leukonychia	White nails	Hypoalbuminemia, chronic renal failure
Terry's Nails	White proximal nail, darker distal nail with ground glass appearance, no lunula	Liver cirrhosis
NAIL FOLD CHANGES		
Herpetic Whitlow	HSV infection of distal phalanx	HSV infection
Paronychia	Local inflammation of the nail fold around the nail bed	Acute: painful infection Chronic: constant wetting (e.g. dishwashing, thumbsucking)
Nail Fold Telangiectasias	Cuticular hemorrhages, roughness, capillary changes	Scleroderma, SLE, dermatomyositis
LOSS OF NAILS		
Temporary Loss	Occurs without scarring	Trauma (especially toenails or fingernails after large subungual hematoma), Beau's lines after severe illness
Permanent Loss	Occurs with scarring	Lichen planus (pterygium), genetic abnormalities (rare)

Adnexal Disorders

HIDRADENITIS SUPPURATIVA

Definition
- a chronic scarring inflammatory skin condition that is a result of follicular occlusion and inflammation within intertriginous zones and areas rich in apocrine glands

Clinical Features
- primary lesions are inflammatory nodules
- presence of sinus formation, clusters of open comedones (double tombstone comedones), and hypertrophic scarring of intertriginous areas
- sites: occurs primarily in the intertriginous areas of the axillae (most common site), inguinal area, inner thighs, perianal and perineal areas, mammary and inframammary regions, buttocks, pubic region, scrotum, vulva, trunk, and occasionally the scalp and retroauricular areas
- additionally significant hyperpigmentation and keloid formation can be seen in more pigmented skin types

Pathophysiology
- follicular occlusion, follicular rupture, and an immune response

Epidemiology
- affects 1-4% of the population, F>M
- onset of symptoms occur between puberty and age 40, typically in 2nd or 3rd decade
- increased incidence in people of African descent
- associated with smoking and excess weight

Differential Diagnosis
- folliculitis, furuncles, carbuncles, acne vulgaris, Crohn's disease, granuloma inguinale, pyoderma gangrenosum, recurrent pilonidal sinus, abscess

Investigations
- clinical diagnosis
- ultrasound can be helpful for disease staging or detecting subclinical disease

Management
- behavioural: avoidance of triggers including shaving or wearing tight fitting clothing, smoking cessation, and weight management, laser hair removal
- pain management with NSAIDs

- mild disease: local therapy with topical antibiotics, topical resorcinol, and intralesional steroids
- moderate to severe disease: antibiotic therapy (oral tetracyclines, clindamycin and rifampin combination, dapsone), oral retinoids, hormonal therapy (metformin, OCPs), surgery (deroofing), laser and light-based therapies (CO_2 laser and Nd:YAG), and biologic therapy
- refractory moderate to severe disease: biologic therapy such as anti-TNFs i.e. adalimumab and infliximab, systemic glucocorticoids, cyclosporine, IV ertapenem, and combination therapies of any of the above treatments

PRIMARY HYPERHIDROSIS

Definition
- secretion of sweat in amounts greater than physiologically needed for thermoregulation

Clinical Features
- focal, visible, excessive sweating of at least 6 mo without apparent cause
- symptoms typically develop during childhood or adolescence and persist throughout life
- symptoms occur only during waking hours (diurnal)
- focal symptoms typically localized to the palms, soles, and axillae, and less commonly the scalp and face

Pathophysiology
- abnormal or exaggerated central response of the eccrine sweat glands to normal emotional stress

Epidemiology
- affects 1-5% of the population
- most patients have a family history of hyperhidrosis

Differential Diagnosis
- excessive heat, medications (e.g. antidepressants, antipyretics, cholinergic agonists, hormonal agents), menopause, and spinal cord injuries (autonomic dysreflexia, orthostatic hypotension, posttraumatic syringomyelia)

Investigations
- clinical diagnosis, iodine starch test

Management
- antiperspirants, botulinum toxin, microwave thermolysis, topical glycopyrronium bromide, suction curettage, systemic agents (oral glycopyrrolate, oral oxybutynin), iontophoresis, or endoscopic thoracic sympathectomy

Oral Diseases

LEUKOPLAKIA
- see *Leukoplakia, D39*

RECURRENT APHTHOUS STOMATITIS

Clinical Features
- also known as "canker sores"
- painful, shallow, typically less than 5 mm in diameter, round to oval shaped, covered by a creamy-white pseudomembrane with an erythematous halo
- sites: labial and buccal mucosa, floor of the mouth, ventral surface of the tongue, soft palate, and oropharyngeal mucosa

Pathophysiology
- dysfunction in the immune system resulting in immunologically mediated damage to epithelial cells
- triggered by trauma, emotional stress, infectious agents, genetic factors, HIV infection, and hormonal fluctuations
- early lesions can show a neutrophilic vessel-based submucosal infiltrate

Epidemiology
- women more commonly affected than men
- peak prevalence in ages 20-30

Differential Diagnosis
- Behçet syndrome, SLE, gluten-sensitive enteropathy, HSV

Investigations
- diagnosis is made clinically

Management
- oral hygiene: soft toothbrush, waxed tape-style dental floss, soft-tipped gum stimulator for plaque removal, and nonalcoholic mouthwash

- reduce traumatic factors inside the mouth such as biting cheeks or lips, and sharp/rough dental restorations
- pain control: lidocaine viscous 2%, diphenhydramine liquid (12.5 mg/5 mL), dyclonine lozenges
- severe refractory cases: colchicine

Skin Manifestations of Systemic Disease

Table 25. Skin Manifestations of Internal Conditions

Disease	Related Dermatoses
AUTOIMMUNE DISORDERS	
Behçet's Disease	Painful aphthous ulcers in oral cavity ± genital mucous membranes, erythema nodosum, acneiform papules
Buerger's Disease	Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital resorptions
Dermatomyositis	Periorbital and extensor violaceous erythema, heliotrope with edema, Gottron's papules (violaceous flat-topped papules with atrophy), periungual erythema, telangiectasia, calcinosis cutis
Polyarteritis Nodosa	Subcutaneous nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livedo reticularis, ulceration
Reactive Arthritis	Keratoderma blennorrhagica (on feet), balanitis circinata (on male penis)
Rheumatic Fever	Petechiae, urticaria, erythema nodosum, rheumatoid nodules, evanescent rash
Sarcoidosis	Heterogeneous cutaneous manifestations ranging from plaques, erythema nodosum, pink, brownish to violaceous nodules/plaques (lupus pernio)
Scleroderma	Raynaud's, non-pitting edema, ulcers, cutaneous calcification, periungual telangiectasia, acrosclerosis, salt-and-pepper pigmentation. Localized scleroderma presenting with waxy/shiny/tense atrophic skin is known as "morphea"
SLE	Malar erythema, discoid rash (erythematous papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy/diffuse alopecia, mucosal ulcers, photosensitivity
Crohn's Disease/UC	Pyoderma gangrenosum, erythema nodosum, Sweet's syndrome
ENDOCRINE DISORDERS	
Addison's Disease	Generalized hyperpigmentation or limited to skin folds, buccal mucosa, and scars
Cushing's Syndrome	Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia
DM	Infections (e.g. boils, carbuncles, candidiasis, S. aureus, dermatophytoses, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipoidica diabeticorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis
Hyperthyroidism	Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropachy, onycholysis
Hypothyroidism	Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows
HIV-RELATED	
Infections	Viral (e.g. HSV, HZV, HPV, CMV, Molluscum contagiosum, oral hairy leukoplakia), bacterial (impetigo, acneiform folliculitis, dental caries, cellulitis, bacillary epithelioid angiomatosis, syphilis), fungal (candidiasis, histoplasmosis, cryptococcus, blastomycosis)
Inflammatory Dermatoses	Seborrhea, psoriasis, pityriasis rosea, vasculitis
Malignancies	Kaposi's sarcoma, lymphoma, BCC, SCC, MM
MALIGNANCY	
Adenocarcinoma Gastrointestinal Cervix/anus/rectum	Peutz-Jeghers: pigmented macules on lips/oral mucosa Paget's disease: eroding scaling plaques of perineum
Carcinoma Breast GI Thyroid Breast/lung/ovary	Paget's disease: eczematous and crusting lesions of the skin of the nipple and usually areola of the breast Palmoplantar keratoderma: thickened skin of palms/soles Sipple's syndrome: multiple mucosal neuromas Dermatomyositis: heliotrope erythema of eyelids and violaceous plaques over knuckles
Lymphoma/Leukemia Hodgkin's Acute leukemia	Ataxia telangiectasia: telangiectasia on pinna, bulbar conjunctiva Ichthyosis: generalized scaling especially on extremities, Sweet's syndrome Bloom's syndrome: butterfly erythema on face, associated with short stature
Multiple Myeloma	Amyloidosis: large, smooth tongue with facial petechiae and waxy papules on eyelids, nasolabial folds, and lips
OTHERS	
Liver Disease	Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry's nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice
Renal Disease	Pruritus, pigmentation, half and half nails, perforating dermatosis, calciphylaxis
Pruritic Urticarial Papules and Plaques of Pregnancy	Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms, and lower back
Cryoglobulinemia	Palpable purpura in cold-exposed areas, Raynaud's, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection

Raynaud's Phenomenon DDx

COLD HAND
Cryoglobulins/Cryofibrinogens
Obstruction/Occupational
Lupus erythematosus, other connective tissue disease
DM/Drugs
Hematologic problems (polycythemia, leukemia, etc.)
Arterial problems (atherosclerosis)
Neurologic problems (vascular tone)
Disease of unknown origin (idiopathic)

Acanthosis Nigricans
An asymptomatic dark thickened velvety hyperpigmentation of flexural skin most commonly peri nuchal. Associated with DM, obesity, and other endocrine disorders, and malignancy. It is a cutaneous marker of tissue insulin resistance

Pediatric Exanthems

• see Pediatrics, P62

Miscellaneous Lesions

Angioedema and Urticaria

Angioedema

- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
  - onset in childhood; 80% have positive family history
  - recurrent attacks; 25% die from laryngeal edema
  - triggers: minor trauma, emotional upset, temperature changes
- types of acquired angioedema
  - acute allergic angioedema (allergens include food, drugs, contrast media, insect venom, latex)
  - non-allergic drug reaction (drugs include ACEI)
  - acquired C1 inhibitor deficiency
- treatment
  - prophylaxis with danazol or stanozolol for hereditary angioedema
  - epinephrine pen to temporize until patient reaches hospital in acute attack

Urticaria

- also known as "hives"
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 h
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen

Table 26. Classification of Urticaria

Type	Etiology
Acute Urticaria >2/3 of cases Attacks last <6 wk Individual lesions last <24 h	Drugs: especially ASA, NSAIDs Foods: nuts, shellfish, eggs, fruit Idiopathic Infection Drugs (antibiotics, hormones, local anesthetics) Foods Parasitic infections Insect stings (bees, wasps, hornets) Physical contact (animal saliva, plant resins, latex, metals, lotions, soap) Direct mast cell release Opiates, muscle relaxants, radio-contrast agents Complement-mediated Serum sickness, transfusion reactions Infections, viral/bacterial (>80% of urticaria in pediatric patients)
Chronic Urticaria <1/3 of cases Attacks last >6 wk Individual lesion lasts <24 h	Idiopathic (90% of chronic urticaria patients) IgE-dependent: trigger associated Aeroallergens Urticarial vasculitis Arachidonic acid metabolism ASA, NSAIDs Physical Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholinergic (hot shower, exercise), solar, pressure (shoulder strap, buttocks), aquagenic (exposure to water), adrenergic (stress), heat Other Mastocytosis, urticaria pigmentosa Parasitic infections Systemic diseases: SLE, endocrinopathy, neoplasm Stress
Urticarial Vasculitis Individual lesions last >24 h Often painful, less likely pruritic, wheals with bruise type lesions Biopsy indicated	Idiopathic Infections Hepatitis Autoimmune diseases SLE Drug hypersensitivity Cimetidine and diltiazem

DDx for Urticaria

MAD HIVES
Malignancy
Allergic
Drugs and foods
Hereditary
Infection
Vasculitis
Emotions
Stings

Approach to Urticaria
- Thorough Hx and physical exam
- **Acute:** no immediate investigations needed; consider referral for allergy testing
- **Chronic:** further investigations required: CBC and differential, urinalysis, ESR, TSH, LFTs to help identify underlying cause
- **Vasculitic:** biopsy of lesion and referral to dermatology

Wheal
- Typically erythematous flat-topped, palpable lesions varying in size with circumscribed dermal edema
- Individual lesion lasts <24 h
- Associated with mast cell release of histamine
- May be pruritic

Mastocytosis (Urticaria Pigmentosa)
Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Darier's sign), due to mast cell degranulation; this occurs within minutes of rubbing

Erythema Nodosum

Clinical Features
- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on extensor lower legs (typically shins), knees, arms
- associated with arthralgia, fever, malaise

Etiology
- 40% are idiopathic
- drugs: sulfonamides, OCPs (also pregnancy), analgesics, all-trans retinoic acid
- infections: GAS, TB, histoplasmosis, Yersinia
- inflammation: sarcoidosis, Crohn's > UC
- malignancy: acute leukemia, Hodgkin's lymphoma

Epidemiology
- 15-30 y/o, F:M=3:1
- lesions last for days and spontaneously resolve in 6 wk

Investigations
- CXR (to rule out chest infection and sarcoidosis)
- throat culture, ASO titre, PPD skin test

Management
- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids, oral potassium iodide
- treat underlying cause

DDx of Erythema Nodosum

NODOSUMM
NO cause (idiopathic) in 40%
Drugs (sulfonamides, OCP, etc.)
Other infections (Group A Strep)
Sarcoidosis
UC and Crohn's
Malignancy (leukemia, Hodgkin lymphoma)
Many Infections

Pruritus

Clinical Features
- a sensation provoking a desire to scratch, with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

Etiology
- dermatologic – generalized
  - asteatotic dermatitis ("winter itch" due to dry skin)
  - pruritus of senescent skin (may not have dry skin, any time of year)
  - infestations: scabies, lice
  - immunoglobulins disease (bullous pemphigoid)
  - drug eruptions: ASA, antidepressants, opiates
  - psychogenic states
- dermatologic – local
  - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin's lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, iron deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumours), non-Hodgkin's lymphoma
  - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis

Investigations
- blood work: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture, and serology for parasites
- biopsy

Management
- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- TCS and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria

DDx of Pruritus

SCRATCHED
Scabies
Cholestasis
Renal
Autoimmune
Tumours
Crazies (psychiatric)
Hematology (polycythemia, lymphoma)
Endocrine (thyroid, parathyroid, iron)
Drugs, Dry skin

Consider biopsy of any non-healing wound to rule out cancer

- phototherapy with UVB or PUVA
- doxepin, amitriptyline
- immunosuppressive agents if severe: steroids and steroid-sparing

Wounds and Ulcers

- see Plastic Surgery, PL8

Sunscreens and Preventative Therapy

Sunburn (Solar Erythema)

- erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
- chronic UVA and UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am-4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

Sunscreens

- under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen
- topical chemical: absorbs UV light
  - requires application at least 15-30 min prior to exposure, should be reapplied every 2 h (more often if sweating, swimming)
  - UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
  - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
- topical physical: reflects and scatters UV light
  - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride, and melanin
  - all are effective against the UVA and UVB spectrum
  - less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
- some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

Management

- sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, TCS)
- antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin

Topical Steroids

Table 27. Potency Ranking of Topical Steroids

Relative Potency	Relative Strength	Generic Names	Trade Names	Usage
Weak	x1	hydrocortisone – 2.5% (1%, 0.5%) available OTC)	Emo Cort® Hydrocort®	Intertriginous areas, children, face, thin skin
Moderate	x3	hydrocortisone 17-valerate – 0.2% desonide mometasone furoate	Westcort® Hydrovalt® Tridesilon® Elocom®	Arm, leg, trunk
Potent	x6	betamethasone – 0.1% 17-valerate – 0.1% amcinonide	Betnovate® Celestoderm – V® Cyclocort®	Body
Very Potent	x9	betamethasone dipropionate – 0.05% fluocinonide – 0.05% halcinonide	Diprosone® Lidex, Topsyn gel® Lyderm® Halog®	Palms and soles
Extremely Potent	x12	clobetasol propionate – 0.05% (most potent) betamethasone dipropionate ointment halobetasol propionate – 0.05%	Dermovate® Diprolene® Ultravate®	Palms and soles

Skin Phototypes (Fitzpatrick)

Phototype	Colour of Skin	Skin's Response to Sun Exposure (without SPF protection)
I	White	Always burns, never tans
II	White	Always burns, little tan
III	White	Slight burn, slow tan
IV	Pale brown	Slight burn, faster tan
V	Brown	Rarely burns, dark tan
VI	Dark brown or black	Never burns, dark tan

SPF = burn time with cream/burn time without cream

UV Radiation

UVA (320-400 nm): Aging
- Penetrates skin more effectively than UVB or UVC
- Responsible for tanning, burning, wrinkling, photoallergy, and premature skin aging
- Penetrates clouds, glass, and is reflected off water, snow, and cement

UVB (290-320 nm): Burning
- Absorbed by the outer dermis
- Is mainly responsible for burning and premature skin aging
- Primarily responsible for BCC, SCC
- Does not penetrate glass and is substantially absorbed by ozone

UVC (200-290 nm)
- Is filtered by ozone layer

Body Site: Relative Percutaneous Absorption

Forearm	1.0
Plantar foot	0.14
Palm	0.83
Back	1.7
Scalp	3.7
Forehead	6.0
Cheeks	13.0
Scrotum	42.0

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption

Side Effects of Topical Steroids

Local: atrophy, perioral dermatitis, steroid acne, rosacea, contact dermatitis, tachyphylaxis (tolerance), telangiectasia, striae, hypertrichosis, hypopigmentation

Systemic: suppression of HPA axis, mood changes, nervousness, insomnia, hyperglycemia, fluid/sodium retention, increased appetite, weight gain, muscular weakness (Note: significant systemic absorption to cause systemic side effects is rare)

Dermatologic Therapies

Table 28. Common Topical Therapies

Drug Name	Dosing Schedule	Indications	Comments
Calcipotriol (Dovonex®)	0.005% cream, ointment, scalp solution, apply bid For maintenance therapy, apply once daily	Psoriasis	Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk >14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)
Imiquimod (Aldara®)	5% cream applied 3x/wk Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water Max duration 16 wk	Genital warts Cutaneous warts AK Superficial BCC	Avoid natural/artificial UV exposure Local skin and application site reactions Erythema, ulceration, edema, flu-like symptoms Works best for warts on mucosal surfaces May induce inflammation and erosion
Permethrin (Kwellada® P Lotion and Nix® Dermal Cream)	1% or 5% cream, applied once overnight to all skin areas from neck down, repeated one wk later	Scabies (Kwellada-P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)	Do not use in children <2 yr Hypersensitivity to drug, or known sensitivity to chrysanthemums Local reactions only (resolve rapidly); including burning, pruritus Low toxicity, excellent results Consider second application after 7 d
Pimecrolimus (Elidel®)	1% cream bid (>3 mo old) Use for as long as lesions persist and discontinue upon resolution of symptoms	AD (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive
Tacrolimus Topical (Protopic®)	0.03% (2-15 y/o) or 0.1% (>15 y/o) ointment bid Continue for duration of disease plus 1 wk after clearing	AD (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive
Crisaborole (Eucrisa®)	> 3 mos of age	AD mild to moderate	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive

Topical Vehicles

Ointment (water in oil): hydrate, greasy

Cream (oil in water): hydrate, variable

Lotion (powder in water): drying, cosmesis

Solutions (water, alcohol, propylene glycol)

Gel (solution that melts on contact with skin, alcohol): drying

Foam is a newer vehicle and several agents are now available in foam vehicles. Examples include Olux-E™ (clobetasol), Verdeso™ (desonide), Luxiq™ (betamethasone), and Enstilar™ (betamethasone propionate and calcipotriol))

Sprays: Lamisil™ (terbinafine) spray, Clobex™ spray (clobetasol)

Lacquers: Penlac® (ciclopirox), Jublia® (efinaconazole)

Deciding on the Amount of Steroid to Use (Adults)

1 palm = 1% BSA

1 fingertip unit (FTU) = amount of topical medication (from 5 mm nozzle) placed on pad of index finger from distal tip to DIP = 500 mg = 2% BSA

Therefore give 30 g for every 2 palms of area to cover (if applying steroid bid, 1 mo supply)

note ¼ to ½ FTU for younger children

Table 29. Common Oral Therapies

Drug Name	Dosing Schedule	Indications	Comments
Acitretin (Soriatane®)	25-50 mg PO once daily; maximum 75 mg/d	Severe psoriasis Other disorders of hyperkeratinization (ichthyosis, Darier's disease)	Monitoring Cr at baseline; LFTs at baseline, then q1-2 wk until stable, then as clinically indicated; fasting lipid panel at baseline, then q1-2 wk until stable, then if long-term treatment or high-risk patient, continue periodically; urine or serum pregnancy test x 2 at baseline, qmo during treatment, then q3 mo for >3 yr after discontinuation; glucose if diabetes; radiography periodically if long-term treatment Contraindications Women of childbearing potential unless strict contraceptive requirements are met Drug interactions Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives May be combined with PUVA phototherapy (known as re-PUVA)
Antivirals	famciclovir (Famvir®) 250 mg PO tid x 7-10 d (for 1st episode of genital herpes) 125 mg PO bid x 3 d (for recurrent genital herpes)	Chickenpox HZV Genital herpes Acute and prophylactic to reduce transmission in infected patients Herpes labialis	Side effects Headache, nausea, diarrhea, abdominal pain Reduce dose if impaired renal function Drug interactions Cladribine, varicella vaccine, zoster vaccine
	valacyclovir (Valtrex®) 1000 mg PO bid x 3 d (for 1st episode of genital herpes) 500 mg PO bid x 5 d (for recurrent genital herpes)		Side effects Dizziness, depression, abdominal pain Reduce dose if impaired renal function Drug interactions cladribine, foscarnet, varicella vaccine, zoster vaccine
Cyclosporine (Neoral®)	2.5-4 mg/kg/d PO divided bid Max 4 mg/kg/d After 4 wk may increase by 0.5 mg/kg/d q2 wk Concomitant dose of magnesium may protect the kidneys	Psoriasis May also be effective in: Lichen planus EM Recalcitrant urticaria Recalcitrant AD	Monitoring BUN/Cr x2 at baseline, then q2 wk x 3 mo, then if stable, qmo; BP x 2, CBC, K+, Mg2+, lipid panel, uric acid at baseline, then q2 wk x 3 mo, then qmo if stable, or more frequently if adjust dose; LFTs Contraindications Abnormal renal function, uncontrolled hypertension, malignancy (except NMSC), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug Long-term effects preclude use of cyclosporine for >2 yr; discontinue earlier if possible May consider rotating therapy with other drugs to minimize adverse effects of each drug

Table 29. Common Oral Therapies

Drug Name	Dosing Schedule	Indications	Comments
Dapsone	50-100-150 mg PO once daily tapering to 25-50 mg PO once daily to as low as 50 mg 2x/wk	Dermatitis herpetiformis, neutrophilic dermatoses	Monitoring G6PD before treatment starts; CBC qwk x 4, qmo x 6, then q6 mo thereafter; LFTs at baseline, then periodically Side effects Neuropathy Hemolysis (Vitamin C and E supplementation can help prevent this) Drug interactions Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major) Often a dramatic response within hours
Doxycycline	100 mg PO bid	Acne vulgaris Rosacea Bullous pemphigoid	Contraindications Pregnancy, hepatic impairment, drug hypersensitivity Taking acitretin, isotretinoin, or penicillin antibiotic Oral typhoid vaccine
Isotretinoin (Accutane®, Clarus®, Epuris®)	0.5-1 mg/kg/d given once daily to achieve a total dose of 120 mg/kg (20-24 wk)	Severe nodular and/or inflammatory acne Acne conglobata Recalcitrant acne Widespread comedonal acne	Monitoring Fasting lipid panel at baseline, then q1-2 wk until lipid response to isotretinoin is established or if risk factors more frequently; LFTs at baseline, then q1-2 wk until stable; pregnancy test x 2 at baseline; glucose frequently if risk factors Contraindications Teratogenic – in sexually active females, 2 forms of reliable contraception necessary Generally regarded as unsafe in lactation Side effects Decreased night vision, decreased tolerance to contact lenses, dry mucous membranes May transiently exacerbate acne, dry skin Depression, myalgia Drug interactions Caution if used at the same time as tetracycline family antibiotics – both may cause pseudotumour cerebri Discontinue vitamin A supplements Drug may be discontinued at 16-20 wk when nodule count has dropped by >70%; a second course may be initiated after 2 mo prn Refractory cases may require >3 courses
Itraconazole (Sporanox®)	100-400 mg PO once daily, depending on infection Tinea corporis/cruris/versicolor: 200 mg PO once daily x 7 d Tinea pedis: 200 mg PO bid x 3 d Toenails: 200 mg PO bid x 3 d once per mo, repeated 3x Fingernail involvement only: 200 mg bid PO x 3 d once per mo	Onychomycosis Tinea corporis, cruris, pedis, versicolor, capitis	Contraindications CHF Side effects Serious hepatotoxicity Drug Interactions Inhibits CYP3A4 Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs) Give capsules with food, capsules must be swallowed whole
Ivermectin (Mectizan®, Stromectol®)	200-250 µg/kg PO weekly x 2 Take once as directed; repeat one wk later	Onchocerciasis (USA only) Not licensed for use in Canada Also effective for: scabies	No significant serious side effects Efficacious
Methotrexate	10-25 mg qwk, PO, IM, or IV Max: 30 mg/wk To minimize side effects, administer with folic acid supplementation: 1-5 mg once daily	Psoriasis AD Lymphomatoid papulosis May also be effective in: cutaneous sarcoidosis	Monitoring Pregnancy test at baseline; CBC at baseline, then q6 mo or more frequently if initial treatment, dose change, elevated serum level risk, or chemotherapy use; BUN/Cr, LFTs at baseline, then q4-8 wk or more frequently if initial Tx, dose change, elevated serum level risk, or chemotherapy use; serum albumin at baseline if psoriasis, then continue periodically; CXR at baseline; liver biopsy at baseline if psoriasis or if RA with history of alcoholism, persistently abnormal baseline LFTs, or chronic HBV or HCV infection, then if psoriasis repeat after total cumulative dose 1.5 g and each additional 1-1.5 g; serum drug levels if renal impairment, or high dose chemotherapy use Contraindications Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy May be combined with cyclosporine to allow lower doses of both drugs
OCPs (TriCyclen®, Diane 35®, Alesse®)	1 pill PO once daily	Hormonal acne (chin, jawline) Acne associated with polycystic ovarian syndrome or other endocrine abnormalities	All combined OCPs are helpful in acne but those listed on the left have undergone RCTs Contraindications Smoking, HTN, migraines with aura, pregnancy Routine gynecological health maintenance should be up to date
Spironolactone	50-100 mg PO once daily alone or with OCPs	Hormonal acne (chin, jawline) Acne with endocrine abnormality	Contraindications Pregnancy Side effects Menstrual irregularities at higher doses if not on OCPs Breast tenderness, mild diuresis common Risk of hyperkalemia – counsel patients to reduce intake of potassium rich foods such as bananas
Terbinafine (Lamisil®)	250 mg PO once daily x 2 wk Fingernails x 6 wk Toenails x 12 wk Confirm diagnosis prior to treatment	Onychomycosis Tinea corporis, cruris, pedis, capitis	Contraindications Pregnancy, chronic or active liver disease Drug interactions Potent inhibitor of CYP2D6; use with caution when also taking β-blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics Drug concentrates rapidly in skin, hair, and nails at levels associated with fungicidal activity
Tetracycline	250-500 mg PO bid to tid Taken 1 h before or 2 h after a meal	Acne vulgaris Rosacea Bullous pemphigoid	Contraindications Severe renal or hepatic dysfunction

Traumatic and Mechanical Disorders

PERNIOSIS

Definition
- abnormal inflammatory response to cold, damp, non-freezing conditions

Epidemiology
- common in the United Kingdom and northwestern Europe; common for those whose homes lack central heating
- women, the elderly, and children are most affected

Clinical Features
- single or multiple erythematous to blue-violet macules, nodules, or papules
- blistering or ulceration seen in severe cases
- lesions present on the distal toes and fingers, and less often on the heels, ears, and nose
- symptoms of burning, itching, or pain, lasting 1-3 wk

Pathophysiology
- unknown but may be associated with cryoglobulins or cold agglutinins

Differential Diagnosis
- chilblain lupus erythematosus, lupus pernio

Treatment
- warming clothing, avoidance of cold, damp conditions, keeping feet dry, smoking cessation
- nifedipine, nicotinamide, phenoxybenzamine, sympathectomy, and erythemogenic UVB phototherapy

TRAUMATIC AURICULAR HEMATOMA (CAULIFLOWER EAR)
- see Plastic Surgery, PL34

ANIMAL BITES
- see *Cellulitis, D30*

BITES
- see Plastic Surgery, PL11

BURN INJURIES
- see Plastic Surgery, PL18

FROSTBITE
- see Emergency Medicine, ER46

KELOIDS
- see *Keloids, D10*

THERMAL INJURY
- see Plastic Surgery, PL18

UV LIGHT INJURIES
- see *Sunscreens and Preventative Therapy, D52*

Landmark Dermatology Trials

Trial Name	Reference	Clinical Trial Details
MELANOMA		
NCT00094653	NEJM 2010; 363:711-723	**Title:** Improved Survival with Ipilimumab in Patients with Metastatic Melanoma **Purpose:** To compare ipilimumab administered with or without a glycoprotein 100 (gp100) peptide vaccine to gp100 alone in patients with previously treated metastatic melanoma. **Methods:** 676 HLA-A*0201–positive patients with unresectable stage III or IV melanoma, were randomized in a 3:1:1 ratio to receive ipilimumab+gp100 (n=403), ipilimumab alone (n=137), or gp100 alone (n=136). **Results:** Median survival was 10 mo among patients receiving ipilimumab plus gp100, as compared with 6.4 mo among patients receiving gp100 alone and 10.1 mo median survival with ipilimumab alone. No significant difference in survival between ipilimumab groups was noted. Grade 3 or 4 immune-related adverse events occurred in 10-15% of patients treated with ipilimumab and 3% treated with gp100 alone. **Conclusions:** Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma.
BRIM-3	NEJM 2011; 364:2507-2516	**Title:** Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation **Purpose:** To compare the efficacy of BRAF kinase inhibitor vemurafenib (PLX4032) vs. dacarbazine in patients with metastatic melanoma. **Methods:** Phase 3 RCT comparing vemurafenib with dacarbazine in 675 patients with untreated, metastatic melanoma with BRAF V600E mutation. Patients were randomized to receive vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg/m2 of body-surface area intravenously every 3 wk). Co-primary endpoints: overall and progression-free survival. **Results:** At 6 mo, overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group. Vemurafenib was associated with a relative reduction of death risk by 63% and a reduction of 74% in the risk of either death or disease progression vs. dacarbazine. Response rates were reported to be 48% for vemurafenib and 5% for dacarbazine. Common adverse events associated with vemurafenib: arthralgia, rash, fatigue, alopecia, keratoacanthoma, photosensitivity, nausea, and diarrhea. **Conclusions:** Vemurafenib improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation.
RELATIVITY-047	NEJM 2022;386:24-34	Title: Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma Purpose: To assess the efficacy of relatlimab (LAG-3-blocking antibody) plus nivolumab (PD-1-blocking antibody) as compared to nivolumab alone on previously untreated metastatic or unresectable melanoma. Methods: Phase 2-3, double-blind, randomized trial of 714 patients with previously untreated stage III or IV metastatic or unresectable melanoma. Patients were randomized to receive relatlimab-nivolumab or nivolumab alone q4 wk. Primary end-point was progression-free survival. Results: Patients receiving relatlimab-nivolumab had a median progression-free survival of 10.1 mo as compared to 4.6 mo in those receiving nivolumab alone (HR, 0.75; 95% CI, 0.62-0.92; p=0.006). Conclusions: Relatlimab plus nivolumab displays greater progression-free survival than nivolumab alone in patients with previously untreated metastatic or unresectable melanoma.
NCT03698019	NEJM 2023;388:813-823	**Title:** Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma **Purpose:** To determine the effect of neoadjuvant and adjuvant pembrolizumab on event-free survival in patients with resectable stage III-IV melanoma as compared to adjuvant therapy alone. **Methods:** Patients with resectable stage IIIB to IVC melanoma (n=313) were randomly assigned to receive neoadjuvant-adjuvant pembrolizumab (before and after surgery) or adjuvant therapy alone (after surgery) for 1 yr, or until the development of toxic effects or disease recurrence. Primary endpoint was event-free survival. **Results:** Event-free survival was significantly longer in patients receiving neoadjuvant-adjuvant pembrolizumab compared to adjuvant therapy alone (p=0.004). Event-free survival was 72% (95% CI, 64-80) and 49% (95% CI, 41-59) in the neoadjuvant-adjuvant and adjuvant groups, respectively. **Conclusions:** Neoadjuvant-adjuvant treatment with pembrolizumab results in longer event-free survival in patients with resectable stage III or IV melanoma than adjuvant treatment alone.
PSORIASIS		
BE VIVID	Lancet 2021, 397: 475-486	**Title:** Bimekizumab versus Ustekinumab for the Treatment of Moderate to Severe Plaque Psoriasis (BE VIVID): Efficacy and Safety from a 52 wk, Multicentre, Double-blind, Active Comparator and Placebo-Controlled Phase 3 Trial **Purpose:** To compare the efficacy and safety of a 52 wk treatment with bimekizumab vs. placebo vs. ustekinumab in patients with moderate to severe plaque psoriasis. **Methods:** Multicentre RCT involving adults 18 yr of age or older with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index [PASI] score ≥12, ≥10% body surface area affected by psoriasis, and Investigator's Global Assessment [IGA] score ≥3 on a five-point-scale). Patients were randomly assigned (4:2:1) to bimekizumab 320 mg every 4 wk, ustekinumab 45 mg or 90 mg at wk 0 and 4, then every 12 wk, or placebo every 4 wk. At 16 wk, patients in the placebo group were switched to bimekizumab. **Results:** The study enrolled 567 patients. At wk 16, 85% of patients in the bimekizumab group had PASI90 vs. 50% in the ustekinumab group, and 5% in the placebo group. Approximately 84% of patients in the bimekizumab group had an IGA response vs. 53% in the ustekinumab group, and 5% in the placebo groups. Major cardiac adverse events occurred in 5 patients with pre-existing CV risk factors in the bimekizumab group, whereas none occurred in the ustekinumab group. Additionally, oral candidiasis rates were higher than placebo and ustekinumab, and one case of IBD was recorded. **Conclusions:** Bimekizumab was more efficacious than ustekinumab and placebo in the treatment of moderate to severe plaque psoriasis. Additional studies may be needed to assess safety.
ADVANCE	J Am Acad Dermatol 2022;86:77-85	**Title:** Efficacy and Safety of Apremilast (Phosphodiesterase Inhibitor) in Patients with Mild-to-moderate Plaque Psoriasis **Purpose:** To evaluate the effectiveness of apremilast in treating mild-to-moderate plaque psoriasis. **Methods:** A phase 3, double-blind, placebo-controlled study was conducted in 595 adults with mild-to-moderate psoriasis. Patients were randomized to either 30 mg twice daily oral apremilast or placebo (oral tablets of no pharmacological significance) for the first 16 wk. The outcome of interest was the achievement of a static Physician Global Assessment score of 0 (clear) or 1 (almost clear). **Results:** A significantly larger proportion of the apremilast group met the desired static Physician Global Assessment response rate when compared to the placebo group (21.6% vs. 4.1%). **Conclusions:** Apremilast proved effective as a treatment for mild-to-moderate plaque psoriasis.

Trial Name	Reference	Clinical Trial Details
ATOPIC DERMATITIS		
ECZTRA	Br J Dermatol 2021;184:450-463	**Title:** Tralokinumab (Monoclonal Antibody) Plus Topical Corticosteroids (TCS) for the Treatment of Moderate-to-severe Atopic Dermatitis **Purpose:** To evaluate the safety and effectiveness of tralokinumab in treating moderate to severe atopic dermatitis. **Methods:** A double-blind placebo study was conducted using 380 patients, 253 of which were randomized to the treatment group (subcutaneous tralokinumab 300 mg every 2 wk with TCS as needed over 16 wk) and the remainder to the placebo group (placebo every 2 wk with TCS as needed over 16 wk). The outcome of interest was a 75% improvement in the Eczema Area and Severity Index (EASI). **Results:** After 16 wk of treatment, there was a significantly larger proportion of patients treated with tralokinumab (56%) that achieved the EASI benchmark when compared to the placebo group (35.7%). **Conclusions:** Tralokinumab in combination with the current standard of care was proven to be effective and well-tolerated in treatment for atopic dermatitis.
ADvocate 1 and ADvocate2	NEJM 2023;388:1080-1091	**Title:** Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis **Purpose:** To assess the efficacy of lebrikizumab, an IL-13 monoclonal antibody, on moderate to severe AD. **Methods:** Two RCTs were conducted (n=379 and n=427) in which adults (≥18 y/o) or adolescents (12-18 y/o) with moderate to severe AD were randomly assigned to receive lebrikizumab or placebo (SC every 2 wk) for 16 wk. Primary outcome was an Investigator's Global Assessment (IGA) score of 0-1 (range 0-4 from clear to severe disease). Secondary outcomes included 75% improvement in the Eczema Area and Severity Index (EASI-75). **Results:** The primary outcome was met in 43.1% and 12.7% of patients on lebrikizumab and placebo, respectively ($p<0.001$). EASI-75 was attained in 58.8% and 16.2% of patients on lebrikizumab and placebo, respectively ($p<0.001$). **Conclusions:** Lebrikizumab is effective in the treatment of moderate to severe AD in adolescent and adult patients.
VITILIGO		
TRuE-V1 & TRuE-V2	NEJM 2022;387:1445-1455	**Title:** Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo **Purpose:** To determine the effect of ruxolitinib cream (JAK1/2 inhibitor) on repigmentation in adults with vitiligo. **Methods:** Two RCTs were conducted (n=330 in TRuE-V1, n=334 in TRuE-V2) in which patients aged >12 with non-segmental vitiligo (≤10% BSA depigmentation) were randomly assigned to receive 1.5% ruxolitinib cream or vehicle control bid for 52 wk. Primary endpoint was a 75% or greater decrease in the facial Vitiligo Area Scoring Index (F-VASI75 response). **Results:** Treatment with ruxolitinib resulted in a F-VASI75 response in 29.8% as compared to 7.8% in controls in TRuE-V1 (RR, 4.0; 95% CI, 1.9 to 8.4; $p<0.001$). Similarly, treatment with ruxolitinib resulted in a F-VASI75 response in 30.9% as compared to 11.4% in controls in TRuE-V2 (RR, 2.7; 95% CI, 1.5 to 4.9; $p<0.001$). Adverse events of application-site acne, nasopharyngitis, and application-site pruritus were observed in 54.8% and 62.3% of patients on ruxolitinib in TRuE-V1 and TRuE-V2 trials, respectively. **Conclusions:** Ruxolitinib cream is superior to vehicle control in the repigmentation of vitiligo in adult patients at 52 wk, but use is associated with application-site adverse events such as acne and pruritus.
ALOPECIA AREATA		
BRAVE-AA1 & BRAVE-AA2	NEJM 2022;386:1687-1699	**Title:** Two Phase 3 Trials of Baricitinib for Alopecia Areata **Purpose:** To assess the efficacy of baricitinib (JAK1/2 inhibitor) on alopecia areata. **Methods:** Two RCTs were conducted (n=654 in BRAVE-AA1, n=546 in BRAVE-AA2) in which adult patients with severe alopecia areata were randomly assigned to receive oral baricitinib 1x daily (2mg or 4mg) or placebo for 36 wk. Primary outcome was assessment of the Severity of Alopecia Tool (SALT) score (range 0-100, no scalp hair loss to complete scalp hair loss). **Results:** In BRAVE-AA1, SALT scores ≤20 were achieved in 38.8% of patients in the 4mg baricitinib group, 22.8% in the 2mg baricitinib group, and 6.2% in the placebo group ($p<0.001$ for each dose vs. placebo). In BRAVE-AA2, SALT scores ≤20 were achieved in 35.9% of patients in the 4mg baricitinib group, 19.4% in the 2mg baricitinib group, and 3.3% in the placebo group ($p<0.001$ for each dose vs. placebo). **Conclusions:** This study suggests that baricitinib is more effective in the hair regrowth of patients with severe alopecia areata as compared to placebo.

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ER Emergency Medicine

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Acronyms

AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ACEI	angiotensin-converting enzyme inhibitor
ACLS	Advanced Cardiac Life Support
ACS	acute coronary syndrome
AED	automatic external defibrillator
AFib	atrial fibrillation
AG	anion gap
AHA	American Heart Association
ARDS	acute respiratory distress syndrome
AVN	avascular necrosis
AVPU	alert, voice, pain, unresponsive
AXR	abdominal x-ray
Bi-PAP	bilevel positive airway pressure
BSA	body surface area
BUN	blood urea nitrogen
CAS	Children's Aid Society
CIWA	Clinical Institute Withdrawal Assessment for Alcohol
CNS	central nervous system
CPAP	continuous positive airway pressure
CPP	cerebral perfusion pressure
CRP	c-reactive protein
CVA	costovertebral angle
CVS	cardiovascular system
D5W	dextrose 5% in water
D10W	dextrose 10% in water
D50W	dextrose 50% in water
D25W	dextrose 25% in water
DGI	disseminated gonococcal infection
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
DRE	digital rectal exam
DT	delirium tremens
DVT	deep vein thrombosis
ED	emergency department
EM	erythema multiforme
ESR	erythrocyte sedimentation rate
ETT	endotracheal tube
FAST	focused assessment with sonography for trauma
FEV1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
GERD	gastroesophageal reflux disease
GCS	Glasgow Coma Scale
HEENT	head eyes ears nose throat
HI	head injury
H&N	head and neck
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICS	intercostal space
INR	international normalized ratio
IVC	inferior vena cava
LBBB	left bundle branch block
LOC	level of consciousness
LP	lumbar puncture
LSD	lysergic acid diethylamide
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MDI	metered dose inhaler
MDMA	methylenedioxy-methamphetamine
MMSE	mini-mental state examination
MVC	motor vehicle collision
NS	normal saline
NSTEMI	non-ST elevation myocardial infarction
PID	pelvic inflammatory disease
PNS	parasympathetic nervous system
POG	plasma osmolar gap
pRBC	packed red blood cells
PT	prothrombin time
PTT	partial thromboplastin time
RAPD	relative afferent pupillary defect
RBBB	right bundle branch block
ROM	range of motion
RPS	rapid primary survey
RSI	rapid sequence induction
rt-PA	recombinant tissue plasminogen activator
RUSH	rapid ultrasound for shock and hypotension
SAH	subarachnoid hemorrhage
SBP	spontaneous bacterial peritonitis
SCI	spinal cord injury
SHoC	sonography in hypotension and cardiac arrest
SJS	Stevens-Johnson syndrome
SNS	sympathetic nervous system
SOB	shortness of breath
SSRI	selective serotonin reuptake inhibitor
SSSS	staphylococcal scalded skin syndrome
STEMI	ST elevation myocardial infarction
TBI	traumatic brain injury
TCA	tricyclic antidepressant
Tdap	tetanus, diphtheria, acellular pertussis
TEN	toxic epidermal necrolysis
TIA	transient ischaemic attack
TSS	toxic shock syndrome
VBG	venous blood gas
VFib	ventricular fibrillation
VTach	ventricular tachycardia
VTE	venous thromboembolism

Patient Assessment/Management

1. Rapid Primary Survey

- **A**irway maintenance with C-spine control
- **B**reathing and ventilation
- **C**irculation (pulses, hemorrhage control)
- **D**isability (neurological status)
- **E**xposure (complete) and Environment (temperature control)
  - continually reassessed during secondary survey
  - changes in hemodynamic and/or neurological status necessitates a return to the primary survey beginning with airway assessment
- **IMPORTANT:** always watch for signs of shock while doing primary survey
- addressing the "ABCs" is the hallmark of the emergency department
  - in the setting of cardiac arrest, the approach changes to the "CABs": chest compressions, airway, and breathing
  - CAB can also be applied in massive trauma situations in the setting of massive blood loss to treat hypovolemic shock

Approach to the Critically Ill Patient
1. Rapid Primary Survey (RPS)
2. Resuscitation (often concurrent with RPS)
3. Detailed Secondary Survey
4. Definitive Care

Signs of Airway Obstruction
- Agitation, confusion, "universal choking sign"
- Respiratory distress
- Failure to speak, dysphonia, stridor
- Cyanosis

A. AIRWAY
- first priority is to secure airway
- assume a cervical injury in every trauma patient and immobilize with collar
- assess ability to breathe and speak
- listen for evidence of airway obstruction (e.g. stridor)
- can change rapidly, therefore reassess frequently
- assess for facial fractures/edema/burns (impending airway collapse)

Airway Management
- anatomic optimization to allow for oxygenation and ventilation

1. Basic Airway Management
- protect the C-spine
- chin lift (if C-spine injury not suspected) or jaw thrust to open the airway
- sweep and suction to clear mouth of foreign material

2. Temporizing Measures
- nasopharyngeal airway (if gag reflex present, i.e. conscious)
- oropharyngeal airway (if gag reflex absent, i.e. unconscious)
- "rescue" airway devices (e.g. laryngeal mask airway, Combitube®)
- especially for children <8 yo, transtracheal jet ventilation through cricothyroid membrane (rarely used and best to consider opting for a definitive airway)

3. Definitive Airway Management
- ETT intubation (with in-line stabilization of C-spine if applicable)
  - orotracheal ± RSI preferred
  - nasotracheal may be better tolerated in conscious patient
- surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
- cricothyroidotomy

Contraindications to Intubation
- see Table 2, Anesthesia, A8
- supraglottic/glottic pathology that would preclude successful intubation
- provider safety: e.g. SARS-CoV-2 (COVID-19) precludes intubation, CPR, and other aerosol generating procedures in the absence of full PPE

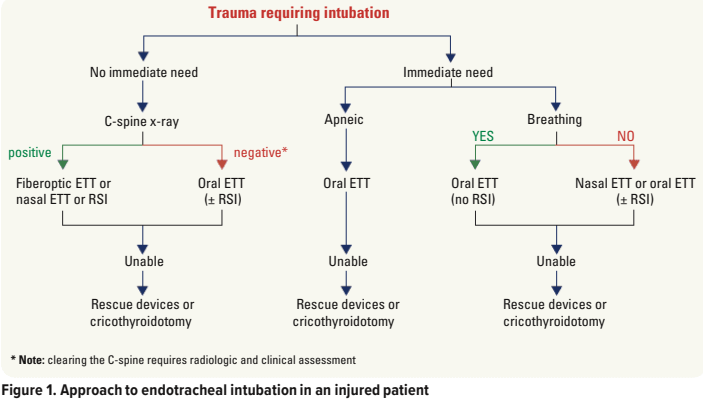


Figure 1. Approach to endotracheal intubation in an injured patient

B. BREATHING

Breathing Assessment
- quantitative measures of respiratory function: rate, oximetry, ABG, A-a gradient
- **Look**
  - mental status (anxiety, agitation, decreased LOC), chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring, increased work of breathing, midline trachea, flail chest
- **Listen**
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping, adventitious sounds (e.g. wheezes, crackles)
- **Feel**
  - tracheal shift, chest wall for crepitus (e.g. subcutaneous emphysema, rib fracture), flail segments, sucking chest wounds

Management of Breathing
- treat likely underlying cause (e.g. bronchodilators, epinephrine, diuresis)
- optimize oxygenation: nasal prongs → simple face mask → venturi mask → non-rebreather mask → high-flow nasal cannula → CPAP/BiPAP (in order of increasing FiO_2)
- bag-valve mask and CPAP to supplement inadequate ventilation

C. CIRCULATION

Definition of Shock
- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities)

Table 1. Major Types of Shock

Hypovolemic	Cardiogenic	Distributive	Obstructive
Hemorrhage (external and internal) Severe burns High output fistulas Dehydration (diarrhea, DKA)	Myocardial ischaemia Dysrhythmias CHF Cardiomyopathies Cardiac valve problems	Septic (see *Sepsis, ER38*) Anaphylactic (see *Anaphylaxis and Allergic Reactions, ER29*) Neurogenic (spinal cord injury)	Cardiac tamponade (see *Chest Trauma, ER11*) Tension pneumothorax (see *Chest Trauma, ER11*) PE (see *Venous Thromboembolism, ER32*) Aortic stenosis Constrictive pericarditis

Clinical Evaluation
- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities (except neurogenic and septic shock), and reduced central venous pressure
- late: hypotension, altered mental status, reduced urine output

Medications that can be Delivered via ETT

NAVEL
Naloxone (Narcan®)
Atropine
Ventolin® (salbutamol)
Epinephrine
Lidocaine

Indications for Intubation (4 P's)
Patent airway
Protects against aspiration (e.g. decreasing GCS <8)
Positive pressure ventilation
Pulmonary toilet (suction)

Rescue Techniques in Intubation
- Bougie (used like a guidewire)
- GlideScope®
- Lighted stylet (uses light through skin to determine if ETT in correct place)
- Fiberoptic intubation (uses fiberoptic cable for indirect visualization)

Video Laryngoscopes

Stylets
Bonfil
Rigid and flexible laryngoscope (RIFL)
SensaScope®

Guide Channels
AirTraq™
Pentax AWS®
Res-Q-Scope II®
Traditional (non-guided)
GlideScope®

Noisy breathing is obstructed breathing until proven otherwise

O_2 Delivery Methods

	FiO_2	Amount Given
Nasal Prongs	25-40%	1-6 L/min
Face Mask	40-60%	5-10 L/min
Non-rebreather	80-90%	15 L/min
High-flow Nasal Cannula	up to 100%	15-60L/min
CPAP/BiPAP	up to 100%	

Shock in a trauma patient is hemorrhagic until proven otherwise

Table 2. Estimation of Degree of Hemorrhagic Shock

Class	I	II	III	IV
Blood Loss	<750 cc	750-1500 cc	1500-2000 cc	>2000 cc
% of Blood Volume	<15%	15-30%	30-40%	>40%
Pulse	<100	>100	>120	>140
Blood Pressure	Normal	Normal	Decreased	Decreased
Respiratory Rate	20	30	35	>45
Capillary Refill	Normal	Decreased	Decreased	Decreased
Urinary Output	30 cc/h	20 cc/h	10 cc/h	None
Fluid Replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

Management of Hemorrhagic Shock

- clear airway and assess breathing either first or simultaneously
- apply direct pressure on external wounds while elevating extremities. Do not remove impaled objects in the emergency room setting as they may tamponade bleeds
- start two large bore (14-16 G) IVs in the brachial/cephalic vein of each arm
- permissive hypotension with pRBC transfusion, ideally crossmatched. If crossmatched blood is unavailable in a timely manner, consider O- for women of childbearing age and O+ for men. Use FFP, platelets or tranexamic acid in early bleeding. If available, activate 'massive transfusion protocol'
- consider common sites of internal bleeding (abdomen, chest, pelvis, long bones, GI tract) where surgical intervention may be necessary

D. DISABILITY

- assess LOC using GCS
- pupils
  - assess equality, size, symmetry, reactivity to light
- unequal or sluggish suggests local eye problem or lateralizing CNS lesion
- non-reactive pupils + decreased LOC: structural cause (especially if asymmetric)
- lateralizing motor deficits

Glasgow Coma Scale

- GCS is for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- most useful if repeated; change in GCS with time is more relevant than the absolute number
- less meaningful for metabolic coma
- patient with deteriorating GCS needs immediate attention
- prognosis based on best post-resuscitation GCS
- reported as a 3-part score: Eyes + Verbal + Motor = Total
- if patient intubated, GCS score reported out of 10 + T (T = tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

Eyes Open		Best Verbal Response		Best Motor Response	
Spontaneously	4	Answers questions appropriately	5	Obeys commands	6
To voice	3	Confused, disoriented	4	Localizes to pain	5
To pain	2	Inappropriate words	3	Withdraws from pain	4
No response	1	Incomprehensible sounds	2	Decorticate (flexion)	3
		No verbal response	1	Decerebrate (extension)	2
				No response	1

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury See *Table 36, ER57 for Modified GCS for infants and children*

E. EXPOSURE/ENVIRONMENT

- expose patient completely and assess entire body for injury; log roll to examine back
- DRE for trauma patients
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

2. Resuscitation

- done concurrently with primary survey
- attend to ABCs
- manage life-threatening problems as they are identified
- vital signs q5-15 min
- ECG, BP, and O_2 monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type

Causes of Shock

SHOCKED
Septic, spinal/neurogenic
Hemorrhagic
Obstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
Cardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)
anaphylactiK
Endocrine (e.g. Addison's, myxedema, coma)
Drugs

Common Sites of Bleeding

- External (e.g. scalp)
- Chest
- Abdomen (peritoneum, retroperitoneum)
- Pelvis
- Long bones
- GI

Fluid Resuscitation

Give bolus until HR decreases, urine output increases, and patient stabilizes

- Maintenance: 4:2:1 rule
- 0-10 kg: 4 cc/kg/h
- 10-20 kg: 2 cc/kg/h
- Remaining weight: 1 cc/kg/h
- Replace ongoing losses and deficits (assume 10% of body weight)

Shortcut for calculating maintenance fluids for any patient ≥20 kg: Fluid rate (in cc/hr) = 40 + patient's weight in kg

Unilateral, Dilated, Non-Reactive Pupil

- Focal mass lesion
- Epidural hematoma
- Subdural hematoma

Contraindications to Foley Insertion

Blood at urethral meatus
Scrotal hematoma
High-riding prostate on DRE

NG Tube Contraindications

Significant mid-face trauma
Basal skull fracture

Table 4. 2010 AHA CPR Guidelines with 2020 Updates

Step/Action	Adult: >8 yr	Child: 1-8 yr	Infant: <1 yr
Airway	Head tilt-chin lift; jaw thrust without head extension if concern for spinal injury		
Breaths	2 breaths at 1 s/breath – stop once see chest rise		
Severe Foreign-Body Airway Obstruction	Abdominal thrust (if conscious)		Back blows and chest compressions
Compressions			
Compression landmarks	In the centre of the chest, lower half of the sternum		Just below nipple line
Compression method: push hard and fast, and allow for complete recoil	2 hands: heel of 1 hand with heel of second hand on top	2 hands: heel of 1 hand with second on top, or 1 hand: heel of 1 hand only	2 fingers, or thumbs
Compression depth	2-2.4 inches	About 1/3 to 1/2 the depth of the chest	
Compression rate	100-120/min with complete chest wall recoil between compressions		
Compression-ventilation ratio	30 compressions to 2 ventilations	15 compressions to 2 ventilations	
Compression-only CPR	Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only		
Defibrillation	Immediate defibrillation if a shockable rhythm (ventricular fibrillation or ventricular tachycardia) is identified Compressions (5 cycles/2 min) and use AED if unwitnessed arrest Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available		

See Anesthesia, *A32 for ACLS Guidelines*

Sodium Bicarbonate Use During Pediatric Cardiopulmonary Resuscitation
Pediatr Crit Care Med 2022;23:784
Purpose: To determine the relationship between sodium bicarbonate use and outcomes during pediatric cardiac arrest.
Methods: Secondary analysis of the prospective, multicenter RCT (ICU-RESUscitation Project) in patients between 37 weeks post-conceptual age and 18 years old who received CPR.
Results: In patients who received sodium bicarbonate, there was a lower survival to hospital discharge (adjusted odds ratio [aOR], 0.7; 95% CI, 0.54–0.92; p = 0.01) and lower survival to hospital discharge with favorable neurologic outcome rates (aOR, 0.69; 95% CI, 0.53–0.91; p = 0.007).
Conclusions: Sodium bicarbonate use in pediatric CPR is associated with poorer outcomes.

3. Secondary Survey

- start after primary survey completed and initial resuscitation and stabilization initiated
- identify other injuries or areas of concern
- full physical exam and CT if indicated by history and exam findings (C-spine, chest, abdomen, and pelvis – required in blunt trauma, consider T-spine and L-spine if indicated)

HISTORY

- "**SAMPLE**": **S**igns and symptoms, **A**llergies, **M**edications, **P**ast medical history, **L**ast meal, **E**vents related to injury or illness

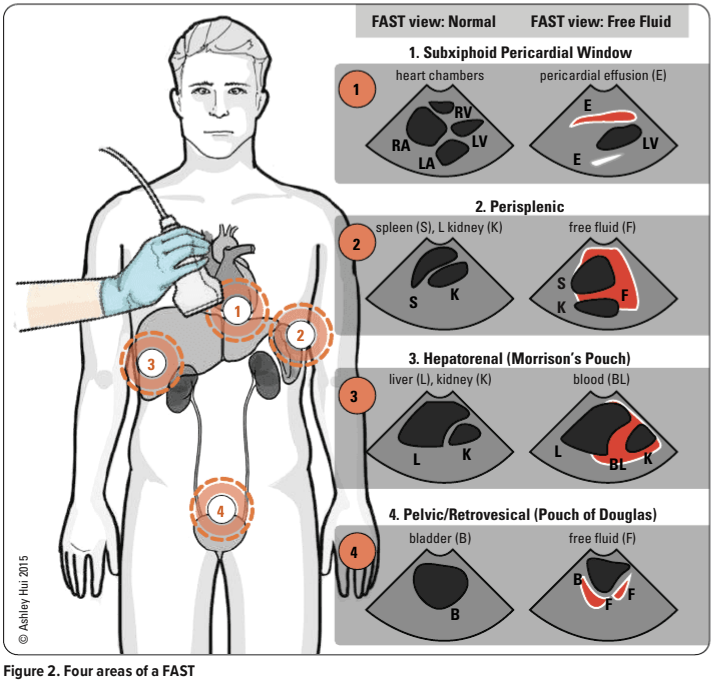


Figure 2. Four areas of a FAST

PHYSICAL EXAM *(see Traumatology, ER7)*

Head and Neck
- inspect for periorbital bruising, mastoid bruising, ocular injuries
- palpate facial bones, scalp
- bite occlusion test with tongue depressor (if patient awake)

Chest
- inspect for equal chest rise, and work of breathing
- auscultate lung fields
- palpate for subcutaneous emphysema, step off and deformities

Abdomen
- assess for peritonitis, abdominal distention, focal areas of tenderness
- DRE for select cases: suspected GI bleed, and in trauma (if pelvic fracture or frank hematuria)

Musculoskeletal
- examine all extremities for swelling, deformity, contusions, tenderness, ROM
- check for pulses (using Doppler probe if not palpable)
- log roll and palpate thoracic and lumbar spines
- palpate iliac crests and pubic symphysis and assess pelvic stability (lateral, AP, vertical)

Neurological
- GCS
- full cranial nerve exam
- assess limb strength and sensation with coarse and fine touch in the cooperative patient
- unconscious patient: assess GCS, breathing pattern, pupils and reaction to light/RAPD, limb tone, reflexes (including corneal and gag), posturing

INITIAL IMAGING
- non-contrast CT head/face/C-spine (rule out fractures and bleeds)
- CXR
- FAST (see *Figure 2, ER5*) or CT abdomen/pelvis (if stable)
- pelvis x-ray

Non-contrast head CT is the best imaging modality for intracranial injury

Consider use of **POCUS** to guide resuscitation

If hypotensive: consider using **RUSH** or **SHoC** protocol

If trauma: use **eFAST**

Ethical Considerations

Consent to Treatment: Adults
- see Ethical, Legal, and Organizational Medicine, ELOM12
- Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury AND obtaining consent is either: a) not possible, OR b) would increase risk to the patient
  - assumes that most people would want to be saved in an emergency
- any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
- be aware of who the legal substitute decision maker (SDM) is and contact them early
- exceptions to the Emergency Rule – treatment cannot be initiated if:
  - a competent patient has previously refused the same or similar treatment and there is no evidence to suggest t he patient's wishes have changed (e.g. after an SDM has been contacted to clarify patient's wishes)
  - an advanced directive is available (e.g. do not resuscitate order), though this is still controversial
  - NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
- if in doubt, initiate treatment
- care can be withdrawn if necessary at a later time or if wishes are clarified by family

Consent to Treatment: Children
- treat immediately if patient is at imminent risk
- parents/guardians have the right to make treatment decisions, unless the child is an emancipated or mature minor (age cut-off varies by province)
- if parents refuse treatment that is considered life-saving or will potentially alter the child's quality of life, act in the best interest of the child, while involving local child protection services and continuing to engage with parents/guardians

Duty to Report
- law may vary depending on province and/or state
- e.g. gunshot wounds, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others

Jehovah's Witnesses
- capable adults have the right to refuse medical treatment
- some patients may decline whole blood, pRBCs, platelets, and plasma, even if considered life-saving
- clarify the use of albumin, immunoglobulins, hemophilic preparations, or other derived products
- parents can refuse care for their child if it is against their belief; evaluate risk of treatment refusal and ensure parents are making an informed decision. If life-saving treatment is refused, can act in the child's interest but will need to involve CAS immediately
- document discussion about treatments, alternatives offered, and potential risks (and their likelihood)

Traumatology

- epidemiology
  - 4.9 million deaths are caused by injuries worldwide (data from 2016)
  - in Canada, traumatic injuries contributed more than 269000 hospitalizations and 17000 deaths (data from 2018)
  - leading cause of death in patients <45 yr
  - 4th highest cause of death in North America
  - causes more deaths in children/adolescents than all diseases combined
- trimodal distribution of death
  - minutes: death usually at the scene from lethal injuries
  - early: death within 4-6 h – "golden hour" (decreased mortality with trauma care)
  - days-weeks: death from multiple organ dysfunction, sepsis, VTE, etc.
- injuries fall into two categories
  - blunt (most common): MVC, pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  - penetrating (increasing in incidence): gunshot wound, stabbing, impalement

Always completely expose and count the number of wounds

Considerations for Traumatic Injury

- important to know the mechanism of injury to anticipate traumatic injuries
- always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- always inquire about HI, loss of consciousness, amnesia, vomiting, headache, and seizure activity

Table 5. Mechanisms and Considerations of Traumatic Injuries

Mechanism of Injury	Special Considerations	Associated Injuries
MVC	Vehicle(s) involved: weight, size, speed, damage Location of patient in vehicle Use and type of seatbelt Ejection of patient from vehicle Entrapment of patient under vehicle Airbag deployment Helmet use in motorcycle collision	Head-on collision: head/facial, thoracic (aortic), lower extremity Lateral/T-bone collision: head, C-spine, thoracic, abdominal, pelvic, and lower extremity Rear-end collision: hyper-extension of C-spine (whiplash injury) Rollover: all of the above may be associated injuries
Pedestrian-Automobile Impact	High morbidity and mortality Vehicle speed is an important factor Site of impact on car	Adults tend to be struck in lower legs (lower extremity injuries), impacted against car (truncal injuries), and thrown to ground (HI)
Falls	Distance of fall: 50% mortality at 4 storeys and 95% mortality at 7 storeys (1 storey = 12 ft = 3.6 m) Landing position (vertical vs. horizontal)	Vertical: lower extremity, pelvic, and spine fractures; HI Horizontal: facial, upper extremity, and rib fractures; abdominal, thoracic, and HI

High-Risk Injuries
- MVC at high speed, resulting in ejection from vehicle
- Motorcycle collisions
- Vehicle vs. pedestrian crashes
- Fall from height >12 ft (3.6 m)

Vehicle vs. Pedestrian Crash

In all patients, don't assume injuries are isolated

Waddell's triad in pediatric patients: Tibia-fibula or femur fracture; Truncal or abdominal injury; Craniofacial injury

Head Trauma

- see Neurosurgery, NS35

ASSESSMENT OF BRAIN INJURY

History
- prehospital status
- mechanism of injury

Physical Exam
- assume C-spine injury until ruled out
- isolated penetrating trauma can forego c-spine mobilization if a neurological exam can be performed
- vital signs
  - shock (not likely due to isolated brain injury, except in infants; assume other injury and/or spinal shock)
  - look for Cushing's response to increasing ICP (bradycardia, HTN, irregular respirations)
- severity of injury determined by
  1. LOC
     - GCS ≤8 intubate, any change in score of 3 or more = serious injury
     - GCS of mild TBI = 13-15, moderate = 9-12, severe = 3-8
  2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
  3. lateralizing signs (motor/sensory)
     - may become subtler with increasing severity of injury
     - reassess frequently

Signs of Increased ICP
- Deteriorating LOC (hallmark)
- Deteriorating respiratory pattern
- Cushing reflex (high BP, low HR, irregular respirations)
- Lateralizing CNS signs (e.g. cranial nerve palsies, hemiparesis)
- Seizures
- Papilledema (occurs late)
- N/V and headache

Signs of Basal Skull Fracture
- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF rhinorrhea/otorrhea

Investigations
- labs: CBC, electrolytes, INR/PTT, glucose, toxicology screen
- CT head (non-contrast) to exclude intracranial hemorrhage/hematoma
- C-spine imaging

Warning Signs of Severe Head Injury
GCS <8
Deteriorating GCS
Unequal pupils
Lateralizing signs
N.B. Altered LOC is a hallmark of brain injury

Management
- goal in ED: reduce secondary injury by avoiding hypoxia, ischaemia, decreased CPP, seizure
- general
  - ABCs
  - ensure oxygen delivery to brain through intubation and prevent hypercarbia
  - maintain BP (sBP >90)
  - treat other injuries
- early neurosurgical consultation for acute and subsequent patient management after imaging
- seizure treatment/prophylaxis
  - phenytoin,levetiracetam
- treat suspected raised ICP
  - intubate (neuroprotective RSI where possible)
  - administer fentanyl or lidocaine at least 2 minutes prior to RSI
  - calm (sedate) if risk for high airway pressures or agitation
  - hyperventilate (100% O_2) to a pCO_2 of 30-35 mmHg
  - elevate head of bed to 20°
  - adequate BP to ensure good cerebral perfusion
  - give mannitol 1g/kg infused rapidly (contraindicated in shock/renal failure) or 3 mL/kg of hypertonic (3%) saline
  - remove c-collar if possible

Disposition
- neurosurgical ICU admission for severe HI
- in a hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
- for minor HI not requiring admission, provide 24 h HI protocol (regular assessment of the patient for signs of loss of consciousness, confusion or amnesia) to competent caregiver, follow up with concussion and/or sports clinic as even seemingly minor HI may cause lasting deficits

Canadian CT Head Rule
Lancet 2001;357:1391-1396
CT Head is only required for patients with minor HI and with any one of the following
- High-Risk (for neurological intervention)
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture
- Vomiting ≥2 episodes
- Age ≥65 yr

Medium-Risk (for brain injury on CT)
- Amnesia before impact >30 min (i.e. cannot recall events just before impact)
- Dangerous mechanism (pedestrian struck by MVC, occupant ejected from motor vehicle, fall from height >3 ft or five stairs)

Minor HI is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.
NB: Canadian CT Head Rule does not apply for non-trauma cases, for GCS <13, ages <16, for patients on Coumadin® and/or having a bleeding disorder, or having an obvious open skull fracture.

Specific Injuries
- fractures
  - Investigation: non-contrast head CT and physical exam

A. skull fractures
- vault fractures
  - suspect if non-frontal injury and/or boggy hematoma
  - linear, non-depressed
    - most common
    - typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
  - depressed
    - open (associated overlying scalp laceration and torn dura, skull fracture disrupting paranasal sinuses or middle ear) vs. closed
- basal skull fractures
  - typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
  - can be a radiological or clinical diagnosis
  - associated with Battle's sign, racoon eyes, hemotympanum, and/or CSF otorrhea/rhinorrhea; though classic signs are often delayed

B. facial fractures (see Plastic Surgery, PL31)
- neuronal injury
- beware of open fracture or sinus fractures (risk of infection)
- severe facial fractures may pose risk to airway from profuse bleeding

- scalp laceration
  - can be a source of significant bleeding
  - achieve haemostasis, inspect and palpate for skull bone defects ± CT head (rule out skull fracture)
- neuronal injury

A. diffuse
- mild TBI = concussion (GCS 13-15, patients are awake, may be confused but able to communicate and follow commands)
  - transient alteration in mental status that may involve loss of consciousness
  - hallmarks of concussion: confusion and amnesia, which may occur immediately after the trauma or minutes later
  - loss of consciousness (if present) must be less than 30 min and post-traumatic amnesia must be less than 24 h
- diffuse axonal injury (requires MRI; diagnosis rarely made in the ED)
  - mild: coma 6-24 h, possibly lasting deficit
  - moderate: coma >24 h, little or no signs of brainstem dysfunction
  - severe: coma >24 h, frequent signs of brainstem dysfunction

B. focal injuries
- contusions
- intracranial hemorrhage (epidural, subdural, intracerebral)

Mild Traumatic Brain Injury

Epidemiology
- TBI results in 1.7 million deaths, hospitalizations, and ED visits each year (US)
- 75% are estimated to be mild TBI; remainder are moderate or severe (see Neurosurgery, NS35)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features
- somatic: headache, sleep disturbance, N/V, blurred vision
- cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
- emotion and behaviour: impulsivity, irritability, depression
- severe symptoms not improving can be a sign of diffuse axonal injury

Extent of retrograde amnesia correlates with severity of injury

Etiology
- falls, MVC, struck by an object, assault, sports

Investigations
- neurological exam
- concussion recognition tool (see parachute.ca)
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

For minor pediatric HI (up to 16 yo with GCS ≥13 and injury within the last 24 h), use Canadian Assessment of Tomography for Childhood Head Injury (CATCH) rule to determine need for CT. CT head required if any of the following findings are exhibited
- GCS <15 at two hours after injury
- Suspected open or depressed skull fracture
- History of worsening headache
- Irritability on examination
- Signs of basal skull fracture
- Hematoma on scalp
- Dangerous mechanism of injury (MVC, fall from ≥3 ft or 5 stairs, fall from bicycle with no helmet)

Treatment
- close observation and follow-up; for patients at risk of intracranial complications, give appropriate discharge instructions to patient and family; watch for changes to clinical features of more severe TBI (see above), and if change, return to ED
- arrange immediate CT and neurological consultation if seizures, bradycardia, hypotension, sluggish pupils and/or focal deficits
- hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
- pharmacological management of pain, depression, headache
- follow Return to Play/Return to Learn guidelines

Prognosis
- most recover with minimal treatment
  - athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life-threatening cerebral edema or permanent impairment

Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck, or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

Every Patient with One or More of the Following Signs or Symptoms should be Placed in a C-Spine Collar
- Midline tenderness
- Neurological symptoms or signs
- Significant distracting injuries
- HI
- Intoxication
- Dangerous mechanism
- History of altered LOC

History
- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

Physical Exam
- ABCs
- abdominal: ecchymosis, tenderness
- neurological: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; log roll, then palpate T-spine and L-spine, assess rectal tone
  - when palpating, assess for tenderness, muscle spasm, bony deformities, step-off, and spinous process malalignment
- extremities: check capillary refill, suspect thoracolumbar injury with calcaneal fractures

Of the investigations, CT is the best modality to assess C-Spine injuries. If unavailable and significant trauma is suspected, protect C-Spine and transfer for definitive imaging. If minor trauma of C-Spine, may consider x-ray imaging

Investigations
- bloodwork: CBC, electrolytes, Cr, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - CT of the spine; if not available, protect spine and transfer for definitive imaging
  - indications
    - unconscious patients (with appropriate mechanism of injury)
    - neurological symptoms or findings
    - deformities that are palpable when patient is log rolled
    - back pain

Cauda Equina Syndrome can occur with any spinal cord injury below T10 vertebrae. Look for incontinence, anterior thigh pain, quadriceps weakness, abnormal sacral sensation, decreased rectal tone, and variable reflexes

- bilateral calcaneal fractures (due to fall from height)
  - concurrent burst fractures of the lumbar or thoracic spine in 10% (T11-L2)
- MRI (for soft tissue injuries) if appropriate (persistent pain, paresthesia, or focal deficits despite normal CT imaging)

Can Clear C-Spine if:

- oriented to person, place, time, and event
- no evidence of intoxication
- no posterior midline cervical tenderness
- no focal neurological deficits
- no painful distracting injuries (e.g. long bone fracture)
- able to rotate neck 45 degrees in each direction without midline tenderness

Management of Cord Injury

- immobilize
- evaluate ABCs
- treat neurogenic shock (maintain sBP >100 mmHg)
- insert NG once facial fractures are excluded (for decompression of paralytic ileus)
- insert Foley catheter (only if no concerns about urethral injury)
- continually reassess high spinal cord injuries as edema can travel up the spine
- if cervical cord lesion, watch for respiratory insufficiency
  - low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact but loss of innervation of intercostals and other accessory muscles of breathing)
  - high cervical cord injury (above C4) may require intubation and ventilation; soft tissue swelling and hematoma can cause airway compromise, therefore low threshold for intubation, even if patient is otherwise well
- if patient is in shock, treat with: volume infusion, consider vasopressors, maintain normothermia and euglycemia

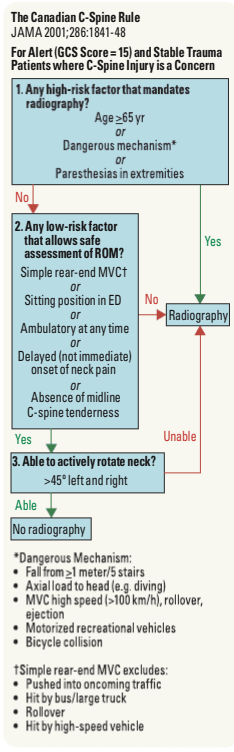
Approach to C-Spine Imaging

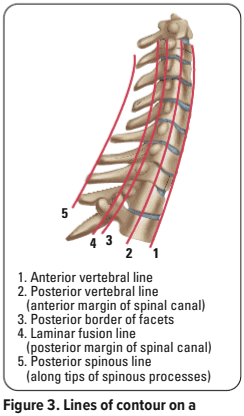
- CT of the spine is the screening modality of choice
- C-Spine CT can detect 97-100% of injuries
- compared to radiography, CT scans allows for more rapid clearance of the C-Spine
- MRI of C-Spine is the preferred technique for soft tissue injuries (spinal cord lesions, intervertebral discs, and spinal ligaments)
- If only C-Spine x-rays are available, radiography can be assessed as follows

Table 6. Interpretation of Lateral View: The ABCS

A	**Adequacy and Alignment** Follow the anterior and posterior contour lines Translation of the vertebra >3.5 mm and angulation of >11 degrees is considered significant for spinal instability Next, follow the spinolaminar line; the diameter between the posterior cortex and the spinolaminar line should be >18 mm Fanning of spinous processes suggests posterior ligamentous disruption Widening of facet joints Check atlanto-occipital joint Line extending inferiorly from clivus should transect odontoid Atlanto-axial articulation, widening of predental space (normal: <3 mm in adults, <5 mm in children) indicates injury of C1 or C2 In children, there is a phenomenon called pseudosubluxation where there is a normal "translation" of C2 on C3 (less often C3 on C4) The translation may be seen in the flexed or neutral position and is not associated with soft tissue swelling (see below) The line of Swischuk is helpful in differentiating pathological cervical spine displacement from pseudosubluxation The line is drawn from the anterior aspect of the posterior arch from C1-C3 The anterior aspect of the posterior arch of C2 should not be more than 2 mm from this line (>2mm is indicative of true subluxation)
B	**Bones** Follow the bony contours of the vertebrae to look for any breaks in the cortex Height, width, and shape of each vertebral body Pedicles, facets, and laminae should appear as one – doubling suggests rotation
C	**Cartilage** Look at the disk spaces to ensure that they are of equal length throughout The anterior and posterior aspect of the individual discs should be equal Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression Measure the pre-dental space (distance from dens to C1 body); it should be <3 mm The distance between the lowest part of the occiput base and the dens should be <2 mm The facet joints should be stacked on top of each other at a 45-degree angle
S	**Soft Tissues** The retropharyngeal space lies anteriorly to the C-Spine; it widens around C4 due to the esophagus The retropharyngeal space normally measures less than 7 mm at C2 and 21 mm at C7; may be wide in children <2 yr on expiration (alternatively, less than the height of the vertebra at C2 and less than the width of the vertebra at C7) Assess retrotracheal spaces (normal: <22 mm at C6-T1, <14 mm in children <5 yr)

- plain films of C-Spine are not reliable in patients with significant trauma and should be used with caution





1. Anterior vertebral line
2. Posterior vertebral line (anterior margin of spinal canal)
3. Posterior border of facets
4. Laminar fusion line (posterior margin of spinal canal)
5. Posterior spinous line (along tips of spinous processes)

Figure 3. Lines of contour on a lateral C-spine x-ray

Prevertebral soft tissue swelling is only 49% sensitive for injury

Sequelae of C-Spine Fractures

- see Neurosurgery, NS38
- acute phase of SCI
  - spinal shock: absence of all voluntary and reflex activity below level of injury
    - decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
    - anal wink or bulbocavernosus reflex more reliable than anal tone, especially in comatose patients
  - neurogenic shock: loss of vasomotor tone, SNS tone
    - watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
    - occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
    - provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
- chronic phase of SCI
  - autonomic dysreflexia: in patients with an SCI at level T6 or above
    - signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
    - common triggers
      - GU causes: bladder distention, urinary tract infection, and kidney stones
      - GI causes: fecal impaction or bowel distension
    - treatment: monitoring and controlling BP, prior to addressing causative issue

Chest Trauma

- two types: those found and managed in 1° survey and those found and managed in 2° survey

Table 7. Life-Threatening Chest Injuries Found in Primary Survey

	Physical Exam	Investigations	Management
Airway Obstruction	Anxiety, stridor, hoarseness, altered mental status Apnea, cyanosis	Do not wait for ABG to intubate	Definitive airway management Intubate early Remove foreign body with magill forceps prior to the intubation. Be prepared for a potential surgical airway
Tension Pneumothorax Clinical diagnosis One-way valve causing accumulation of air in pleural space	Respiratory distress, tachycardia, hypoxia, distended neck veins, cyanosis, asymmetry of chest wall motion Tracheal deviation away from pneumothorax Percussion hyperresonance Unilateral absence of breath sounds	Non-radiographic diagnosis	Needle thoracostomy – large bore needle, 2nd ICS mid clavicular line or finger thoracostomy. Definitive management is a chest tube
Open Pneumothorax Air entering chest from wound rather than trachea	Gunshot or other wound (hole >2/3 tracheal diameter) ± exit wound Unequal breath sounds	ABG: decreased pO_2	Air-tight dressing sealed on 3 sides Chest tube Surgery
Massive Hemothorax >1500 cc blood loss in chest cavity	Pallor, flat neck veins, shock Unilateral dullness Absent breath sounds Hypotension	Usually only able to do supine CXR – entire lung appears radiopaque as blood spreads out over posterior thoracic cavity	Restore blood volume Chest tube Thoracotomy if: >1500 cc total blood loss ≥200 cc/h continued drainage
Flail Chest Free-floating segment of chest wall due to >2 rib fractures, each at 2 sites Underlying lung contusion (cause of morbidity and mortality)	Paradoxical movement of flail segment Palpable crepitus of ribs Decreased air entry on affected side	VBG: decreased pO_2, increased pCO_2 CT: rib fractures, lung contusion	
Cardiac Tamponade Clinical diagnosis Pericardial fluid accumulation impairing ventricular function	Penetrating wound (usually) Beck's triad: hypotension, distended neck veins, muffled heart sounds Tachycardia, tachypnea Kussmaul's sign (increased JVP with inspiration)	Echocardiogram FAST	

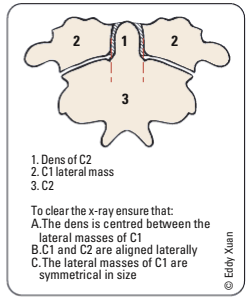

2
1
2
3
1. Dens of C2
2. C1 lateral mass
3. C2
To clear the x-ray ensure that:
A. The dens is centred between the lateral masses of C1
B. C1 and C2 are aligned laterally
C. The lateral masses of C1 are symmetrical in size
© Eddy Xuan

Figure 4. C-spine x-ray; odontoid view

Cardiac Box: sternal notch, nipples, and xiphoid process; penetrating injuries inside this area should increase suspicion of cardiac injury

Supine Oblique Views

Rarely used

Better visualization of posterior element fractures (lamina, pedicle, facet joint)

Good to assess patency of neural foramina

Can be used to visualize the C7-T1 junction

20% of C-spine fractures are accompanied by other spinal fractures, so ensure thoracic and lumbar spine CT is normal before proceeding to OR

Trauma to the chest accounts for 50% of trauma deaths

80% of all chest injuries can be managed non-surgically with simple measures such as intubation, chest tubes, and pain control

3-way Seal for Open Pneumothorax (i.e. sucking chest wound)
Allows air to escape during the expiratory phase (so that you do not get a tension pneumothorax) but seals itself to allow adequate breaths during the inspiratory phase

Pulsus Paradoxus: a drop in BP of >10 mmHg with inspiration. Recall that BP normally drops with inspiration, but what's "paradoxical" about this is that it drops more than it should

Table 8. Potentially Life-Threatening Chest Injuries Found in Secondary Survey

	Physical Exam	Investigations	Management
Pulmonary Contusion	Blunt trauma to chest Interstitial edema impairs compliance and gas exchange	CT: areas of opacification of lung within 6 h of trauma	Maintain adequate ventilation Monitor with ABG, pulse oximeter, and ECG Chest physiotherapy Positive pressure ventilation if severe
Ruptured Diaphragm	Blunt trauma to chest or abdomen (e.g. high lap belt in MVC)	CXR: abnormality of diaphragm/lower lung fields/NG tube placement CT scan and endoscopy: sometimes helpful for diagnosis Laparoscopy for definite diagnosis	Laparotomy for diaphragm repair and associated intra-abdominal injuries
Esophageal Injury	Usually penetrating trauma (pain out of proportion to degree of injury) or caustic ingestion	CXR: mediastinal air (not always) Esophagram (Gastrografin®) Flexible esophagoscopy	Early repair (within 24 h) improves outcome)
Aortic Tear 90% tear at subclavian (near ligamentum arteriosum), most die at scene Salvageable if diagnosis made rapidly	Sudden high speed deceleration (e.g. MVC, fall, airplane crash), complaints of chest pain, dyspnea, hoarseness (frequently absent) Decreased femoral pulses, differential arm BP (arch tear)	CXR, CT scan, transesophageal echocardiogram, aortography (gold standard)	Thoracotomy (may treat other severe injuries first)
Blunt Myocardial Injury (rare)	Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose) Physical exam: overlying injury (e.g. fractures, chest wall contusion)	ECG: dysrhythmias, ST changes Cardiac blood work (e.g. troponin) 2-D Echo: Can assess for tamponade, wall motion, valve function, or thrombi Patients with a normal ECG, normal troponin, and normal hemodynamics rarely get dysrhythmias	O2 Antidysrhythmic agents Analgesia

Other Potentially Life-Threatening Injuries Related to the Chest

Penetrating Neck Trauma

- includes all penetrating trauma to the three zones of the neck
- management: injuries deep to platysma require further evaluation by angiography, contrast CT, or surgery
- do not explore penetrating neck wounds except in the OR

Airway Injuries

O2 + fluid therapy + pain control
Judicious fluid therapy in absence of systemic hypotension
Positive pressure ventilation
± intubation and ventilation if persistently hypoxic or unable to ventilate

IV fluids
Open thoracotomy

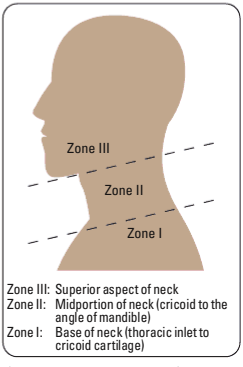
- always maintain a high index of suspicion
- larynx
  - history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma, inhalational injury (e.g. burns)
  - triad: hoarseness, subcutaneous emphysema, palpable fracture
  - other symptoms: hemoptysis, dyspnea, dysphonia
  - investigations: CXR, CT scan, arteriography (if penetrating), CT angiography of the neck
  - management
    - airway: manage early because of edema; if comfortable, can intubate through defect
    - C-spine may also be injured, consider mechanism of injury
    - surgical: tracheotomy vs. repair
- trachea/bronchus
  - frequently missed
  - history: deceleration, penetration, increased intrathoracic pressure, complaints of dyspnea, hemoptysis
  - examination: subcutaneous emphysema, Hamman's sign (crunching sound synchronous with heartbeat)
  - CXR: mediastinal air, persistent pneumothorax, or persistent air leak after chest tube inserted for pneumothorax
  - management
    - surgical repair if >1/3 circumference

Ruptured diaphragm is more often diagnosed on the left side, as the liver conceals right side defects

Aortic Tear

ABC WHITE
X-ray features of **A**ortic tear
Depressed left mainstem **B**ronchus
pleural **C**ap
Wide mediastinum (most consistent)
Hemothorax
Indistinct aortic knuckle
Tracheal deviation to right side
Esophagus (NG tube) deviated to right
(Note: these features are present in 85% of cases, but cannot rule out if absent)

If Penetrating Neck Trauma Present, DON'T:
- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaled object



Zone III: Superior aspect of neck
Zone II: Midportion of neck (cricoid to the angle of mandible)
Zone I: Base of neck (thoracic inlet to cricoid cartilage)

Figure 5. Zones of the neck in trauma

Abdominal Trauma

- two mechanisms
  - blunt: usually causes solid organ injury (spleen = most common, liver = second most common)
  - penetrating: usually causes hollow organ injury or liver injury (most common)

BLUNT TRAUMA

- results in two types of hemorrhage: intraperitoneal and retroperitoneal
- adopt high clinical suspicion of bleeding in multi-system trauma

History

- mechanism of injury, SAMPLE history

Physical Exam

- often unreliable in multi-system trauma, wide spectrum of presentations
  - slow blood loss not immediately apparent
  - tachycardia, tachypnea, oliguria, febrile, hypotension
  - other injuries may mask symptoms
  - serial examinations are required
- abdomen
  - inspect: contusions, abrasions, seat-belt sign, distention
  - auscultate (rare): bruits, bowel sounds
  - palpate: tenderness, rebound tenderness, rigidity, guarding
  - DRE: rectal tone, blood, bone fragments, prostate location
  - placement of NG and Foley catheter should be considered part of the abdominal exam
- assess each system, including cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

Investigations

- labs: CBC, electrolytes, coagulation, fibrinogen, cross and type, glucose, Cr, CK, lipase, amylase, liver enzymes, VBG, blood EtOH, β-hCG, U/A, toxicology screen

Table 9. Imaging in Abdominal Trauma

Imaging	Strengths	Limitations
Ultrasound: FAST	Identifies presence/absence of free fluid in peritoneal cavity RAPID exam: less than 5 min Can also examine pericardium and pleural cavities Can do serial examinations quickly	NOT used to identify specific organ injuries If patient has ascites, FAST will be falsely positive False negatives with small amounts of blood, retroperitoneal blood, delayed presentations, prior abdominal surgery, or incorrect positioning Technically difficult if patient is obese
X-Ray	Chest (looking for free air under diaphragm, diaphragmatic hernia, air-fluid levels), pelvis, cervical, thoracic, lumbar spines	Soft tissue not well visualized
CT Scan	Most specific test	Radiation exposure 20x more than x-ray Use with caution if hemodynamic instability: decide in trauma bay if patient should go directly to the OR (if unstable and FAST +'ve) or is stable enough to go to the CT scanner
Diagnostic Peritoneal Lavage (rarely used)	Most sensitive test Tests for intraperitoneal bleed	Cannot test for retroperitoneal bleed or diaphragmatic rupture Cannot distinguish lethal from trivial bleed Results can take up to 1 h

- imaging must be done if:
  - equivocal abdominal examination, altered sensorium, or distracting injuries (e.g. head trauma, spinal cord injury resulting in abdominal anesthesia)
  - unexplained shock/hypotension
  - patients have multiple traumas and must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
  - fractures of lower ribs, pelvis, spine
  - positive FAST

Management

- general: ABCs, early blood products, and stabilization
- surgical: watchful waiting vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion of injury: admit and observe for 24 h

PENETRATING TRAUMA

- high-risk of gastrointestinal perforation and sepsis
- high risk of cardiac injury if wound is in the cardiac box
- history: size of blade, calibre/distance from gun, route of entry

Seatbelt Injuries May Cause
- Retroperitoneal duodenal trauma
- Intraperitoneal bowel transection
- Mesenteric injury
- L-spine injury

Indications for Foley and NG Tube in Abdominal Trauma
Foley Catheter: unconscious or patient with multiple injuries who cannot void spontaneously
NG Tube: used to decompress the stomach and proximal small bowel. Contraindicated if suspected facial or basal skull fractures

Point-of-Care Ultrasonography for Diagnosing Thoracoabdominal Injuries in Patients with Blunt Trauma
Cochrane DB Syst Rev 2018:CD012669
Purpose: Determine the diagnostic accuracy of POCUS for detecting and excluding free fluid, organ injuries, vascular lesions, and other injuries compared to diagnostic reference standards in patients with blunt trauma.
Methods: Systematic review of prospective or retrospective diagnostic cohort studies of patients with any type of blunt trauma.
Results: 34 studies, 8635 participants. For abdominal trauma, POCUS had a sensitivity of 0.68 (95% CI 0.59-0.75) and a specificity of 0.95 (95% CI 0.92-0.97). In children, pooled sensitivity of POCUS was 0.63 (95% CI 0.46-0.77), as compared to 0.78 (95% CI 0.69-0.84) in an adult/mixed population. For chest injuries, POCUS had a sensitivity of 0.96 (95% CI 0.88-0.99) and a specificity of 0.95 (95% CI 0.97-1.00).
Conclusions: In patients with blunt thoracoabdominal trauma, positive POCUS findings are helpful for guiding treatment decisions. However, with regard to abdominal trauma, a negative POCUS does not rule out injuries and must be verified. This is of particular importance in pediatric trauma, where the sensitivity of POCUS is poor. Based on a small number of studies in a mixed population, POCUS may have a higher sensitivity in chest injuries.

Laparotomy is Mandatory if Penetrating Trauma and:
- Shock
- Peritonitis
- Evisceration
- Free air in abdomen
- Blood in NG tube, Foley catheter, or on DRE

"Rule of Thirds" for Stab Wounds
1/3 do not penetrate peritoneal cavity
1/3 penetrate but are harmless
1/3 cause injury requiring surgery

- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  - thoracoabdominal region (may cause pneumothorax)
  - back or flanks (muscles too thick)

Management
- general: ABCs, fluid resuscitation, and stabilization
- gunshot wounds may require laparotomy if signs of peritonitis, hemodynamic instability or hematemesis

Genitourinary Tract Injuries

- see Urology, U35

Etiology
- blunt trauma: often associated with pelvic fractures
  - upper tract
    - renal
      - contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
      - parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
    - ureter: rare, at uretero-pelvic junction
  - lower tract
    - bladder
      - extraperitoneal rupture of bladder from pelvic fracture fragments
      - intraperitoneal rupture of bladder from trauma and full bladder
    - urethra
      - posterior urethral injuries: MVCs, falls, pelvic fractures
      - anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
  - external genitalia
- penetrating trauma
  - damage to: kidney, bladder, ureter (rare), external genitalia
- acceleration/deceleration injury
  - renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
- iatrogenic
  - ureter and urethra (from instrumentation)

History
- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension

Physical Exam
- abdominal pain, flank pain, CVA tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen
- urethral injury: perineal ecchymosis, blood at penile/urethral meatus, high riding prostate, pelvic fractures

Investigations
- urethra: retrograde urethrography
- bladder: U/A, CT scan, urethrogram ± retrograde cystoscopy ± cystogram (distended bladder + post-void)
- ureter: retrograde urethrogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram

Gross hematuria suggests bladder injury

Management
- urology consult
- renal
  - minor injuries: conservative management
    - bed rest, hydration, analgesia, antibiotics
  - major injuries: admit
    - conservative management with frequent reassessments, serial U/A ± re-imaging
    - surgical repair (exploration, nephrectomy): hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis

In the case of gross hematuria, the genitourinary system is investigated from distal to proximal (i.e. urethrogram, cystogram, etc.)

- ureter
  - ureteroureterostomy
- bladder
  - extraperitoneal
    - minor rupture: Foley drainage x 10-14 d
    - major rupture: surgical repair
  - intraperitoneal: surgical repair
- urethra
  - anterior: conservative, if cannot void, Foley or suprapubic cystostomy and antibiotics
  - posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair

Orthopedic Injuries

- see Orthopedic Surgery *(see Shoulder OR12, Knee OR34, Wrist OR23, Pelvis OR29, Ankle OR41)*

Goals of ED Treatment

- diagnose potentially life/limb-threatening injuries
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

History

- use SAMPLE, mechanism of injury may be very important

Physical Exam

- look (inspection): "SEADS" = swelling, erythema, atrophy, deformity, and skin changes (e.g. bruises)
- feel (palpation): all joints/bones for local tenderness, swelling, warmth, crepitus, joint effusions, and subtle deformity
- move: joints affected plus those above and below injury – active ROM preferred to passive
- neurovascular status: distal to injury (before and after reduction)

LIFE- AND LIMB-THREATENING INJURIES

Table 10. Life- and Limb-Threatening Orthopedic Injuries

Life-Threatening Injuries (usually blood loss)	Limb-Threatening Injuries (usually interruption of blood supply)
Major pelvic fractures	Fracture/dislocation of ankle (talar AVN)
Traumatic amputations	Crush injuries
Massive long bone injuries and associated fat emboli syndrome	Compartment syndrome
Vascular injury proximal to knee/elbow	Open fractures
	Dislocations of knee/hip
	Fractures above knee/elbow

Open Fractures

- communication between fracture site and external surface of skin – increased risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- standard of care is to secure definitive surgical management within 6 h, time to surgery may vary from case-to-case

Vascular Injuries

- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

Compartment Syndrome

- when the intracompartmental pressure within an anatomical area (e.g. forearm or lower leg) exceeds the capillary perfusion pressure, eventually leading to muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - tense compartment
  - look for "The 6 Ps" (note: radial pulse pressure is 120/80 mmHg while capillary perfusion pressure is 30 mmHg, seeing any of the 6 Ps indicates advanced compartment syndrome, therefore do not wait for these signs to diagnose and treat)
  - in the unconscious patient, a Stryker compartment pressure monitor can be used
- requires prompt decompression: remove constrictive casts, dressings; emergent fasciotomy may be needed

Description of Fractures

SOLARTAT
Site
Open vs. closed
Length
Articular
Rotation
Translation
Alignment/**A**ngulation
Type e.g. Salter-Harris, etc.

Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the ED
JAMA 2017;318:1661-1667
Purpose: To compare the efficacy of 4 analgesics on acute extremity pain.
Methods: RCT including 416 patients with moderate to severe acute extremity pain. Participants received ibuprofen 400 mg and acetaminophen 1000 mg; oxycodone 5 mg and acetaminophen 325 mg; hydrocodone 5 mg and acetaminophen 300 mg; or codeine 30 mg and acetaminophen 300 mg. The primary outcome was the difference in decline in pain 2 h after ingestion. Pain was assessed using an 11-point numerical rating scale (NRS).
Results: At 2 h, the mean NRS pain score decreased by 4.3 in the ibuprofen and acetaminophen group; by 4.4 in the oxycodone and acetaminophen group; by 3.5 in the hydrocodone and acetaminophen group; and by 3.9 in the codeine and acetaminophen group (P=0.053).
Conclusions: For patients presenting to the ED with acute extremity pain, there were no statistically significant or clinically important differences in pain reduction at 2 h among single-dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics.

When Dealing with an Open Fracture, Remember "STAND"

Splint
Tetanus prophylaxis
Antibiotics
Neurovascular status (before and after)
Dressings (to cover wound)

Vascular injury/compartment syndrome is suggested by "The 6 Ps" Injury Compartment Syndrome -

6 Ps
Pulse discrepancies
Pallor
Paresthesia/hypoesthesia
Paralysis
Pain (especially when refractory to usual analgesics)
Polar (cold)

UPPER EXTREMITY INJURIES

- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
  - many techniques for reduction (e.g. traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with orthopedics
  - with forceful injury, look for fracture
- Colles' fracture
  - distal radius fracture with dorsal displacement from "Fall on Outstretched Hand" (FOOSH)
  - anteroposterior film: radial shortening, radial deviation, radial displacement
  - lateral film: dorsal displacement, volar angulation
  - reduce, immobilize with splint, out-patient follow-up with orthopedics or immediate orthopedic referral if complicated fracture
  - if involvement of articular surface, consider outpatient fracture clinic or orthopedic referral if unsatisfactory reduction in ED
- scaphoid fracture
  - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
  - negative x-ray: thumb spica splint, repeat x-ray in 1 wk ± CT scan/bone scan
  - positive x-ray: thumb spica splint x 6-8 wk, repeat x-ray in 2 wk
  - treat based on clinical suspicion even in absence of radiological scaphoid fracture
  - risk of AVN of scaphoid if not immobilized
  - outpatient orthopedic follow-up

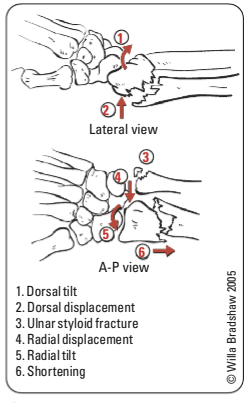


Figure 6. Colles' fracture

LOWER EXTREMITY INJURIES

- knee injuries
  - see *Ottawa Knee Rules*
- pelvic injuries (see Orthopedic Surgery, OR29)
- ankle and foot fractures
  - see *Ottawa Ankle and Foot Rules*
- avulsion of the base of 5th metatarsal
  - occurs with inversion injury
  - supportive tensor or below knee walking cast for 3 wk
- calcaneal fracture
  - associated with fall from height
  - associated with axial loading (other injuries may involve ankles, knees, hips, pelvis, lumbar spine)

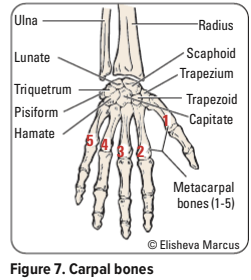


Figure 7. Carpal bones

A knee x-ray examination is required only for acute injury patients with one or more of:

- Age 55 yr or older
- Tenderness at head of fibula
- Isolated tenderness of patella
- Inability to flex to 90°
- Inability to bear weight both immediately and in the ED (four steps)

Figure 8. Ottawa knee rules
Adapted from: Stiell IG, Wells GA, Hoag RH, et al. JAMA 1997;278:2075-2079.

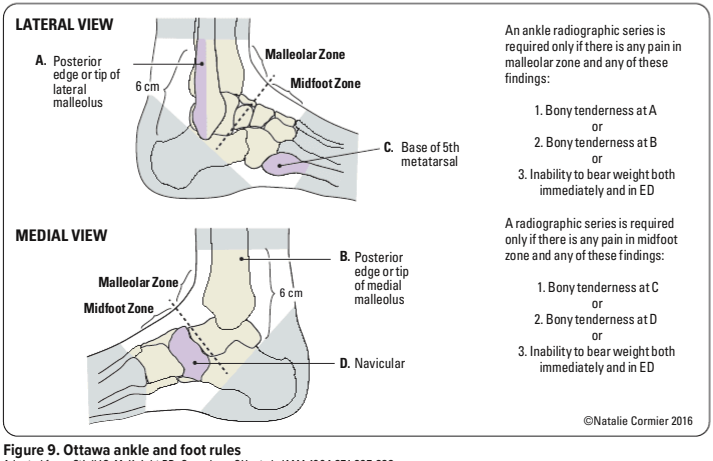

LATERAL VIEW
A. Posterior edge or tip of lateral malleolus
6 cm
Malleolar Zone
Midfoot Zone
C. Base of 5th metatarsal
MEDIAL VIEW
Malleolar Zone
Midfoot Zone
6 cm
B. Posterior edge or tip of medial malleolus
D. Navicular
An ankle radiographic series is required only if there is any pain in malleolar zone and any of these findings:
1. Bony tenderness at A
or
2. Bony tenderness at B
or
3. Inability to bear weight both immediately and in ED
A radiographic series is required only if there is any pain in midfoot zone and any of these findings:
1. Bony tenderness at C
or
2. Bony tenderness at D
or
3. Inability to bear weight both immediately and in ED
©Natalie Cormier 2016

Figure 9. Ottawa ankle and foot rules
Adapted from: Stiell IG, McKnight RD, Greenberg GH, et al. JAMA 1994;271:827-832.

Wound Management

Goals of ED Treatment

- identify injuries and stop any active bleeding – direct pressure
- manage pain
- wound examination and exploration
- cleansing ± antibiotic and tetanus prophylaxis
- closure and dressing

Tetanus Prophylaxis

- both tetanus toxoid (Td) and immunoglobulin (TIG) are safe in pregnancy

Table 11. Guidelines for Tetanus Prophylaxis for Wounds

Vaccination History	Clean, Minor Wounds		All Other Wounds*	
	Tdap or Td†	TIG	Tdap or Td†	TIG
Unknown or fewer than 3 doses	Yes	No	Yes	Yes
3 or more doses	No§	No	No¶	No

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite
†Tdap is preferred to Td for adults who have never received Tdap. Single antigen tetanus toxoid (TT) is no longer available in the United States
§Yes, if more than ten years since the last tetanus toxoid-containing vaccine dose
¶Yes, if more than five years since the last tetanus toxoid-containing vaccine dose
Source: MMWR 1991;40(No. RR-10):1-28

Bruises

- non-palpable = ecchymosis
- palpable collection (not swelling) = hematoma following blunt trauma
- assess for coagulopathy (e.g. liver disease), anticoagulant use

Abrasions

- partial to full thickness break in skin
- management
  - clean thoroughly with brush to prevent foreign body impregnation ± local anesthetic antiseptic ointment (Polysporin® or Vaseline®) for 7 d ± tetanus prophylaxis

Lacerations

- see Plastic Surgery, PL8, sidebar PL24
- consider every structure deep to a laceration injured until proven otherwise
- in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury
- physical exam
  - think about underlying anatomy
  - examine tendon function actively against resistance and neurovascular status distally
  - clean and explore under local anesthetic; look for partial tendon injuries
  - x-ray or U/S wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radiopaque), or if suspect intra-articular involvement
- management
  - disinfect skin/use sterile techniques
  - irrigate copiously with normal saline or tap water
  - analgesia ± anesthesia
  - maximum dose of lidocaine
    - 7 mg/kg with epinephrine
    - 5 mg/kg without epinephrine
- in children, topical anesthetics such as LET (lidocaine, epinephrine, and tetracaine), distraction provided by Child Life Specialist or parent; and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
- secure hemostasis
- evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
- ± prophylactic antibiotics (consider for animal/human bites, intra-oral lesion, or puncture wounds to the foot)
- suture unless: delayed presentation (>24 h), puncture wound, mammalian bite, crush injury, or retained foreign body
- take into account patient and wound factors when considering suturing
- advise patient when to have sutures removed
- cellulitis and necrotizing fasciitis (see Plastic Surgery, PL16)

Acute Treatment of Contusions

RICE
Rest
Ice
Compression
Elevation

High-Risk Factors for Infection
Wound Factors
- Puncture wounds
- Crush injuries
- Wounds >12 h old
- Hand or foot wounds

Patient Factors
- Age >50 yr
- Prosthetic joints or valves (risk of endocarditis)
- Immunocompromised

Suture Use and Duration

Suture to:	Close with Nylon or Other Non-absorbable Suture	Approx. Duration (d)
Face	6-0 or 5-0	5
Not Joint	4-0	7
Joint	3-0	10
Scalp	4-0	7
Mucous Membrane	Absorbable (vicryl)	N/A

N.B. Patients on steroid therapy may need sutures for longer periods of time

Early wound irrigation and debridement are the most important factors in decreasing infection risk

Alternatives to Sutures
Tissue glue
Steristrips®
Staples

Approach to Common ED Presentations

Abdominal Pain

Table 12. Selected Differential Diagnosis of Abdominal Pain

	Emergent	Usually Less Emergent
GI	Perforated viscus, bowel obstruction, ischaemic bowel, appendicitis, strangulated hernia, IBD flare, esophageal rupture, peptic ulcer disease	Diverticulitis, gastroenteritis, GERD, esophagitis, gastritis, IBS
Hepatobiliary	Hepatic/splenic injury, pancreatitis, cholangitis, spontaneous bacterial peritonitis	Biliary colic, cholecystitis, hepatitis
Genital	Female: Ovarian torsion, ectopic pregnancy, tubo-ovarian abscess Male: Testicular torsion	Female: PID, ovarian cyst, salpingitis, endometriosis Male: epididymitis, prostatitis, orchitis
Urinary	Pyelonephritis	Renal colic, cystitis
CVS	MI, aortic dissection, ruptured AAA	Pericarditis
Respirology	PE, empyema	Pneumonia
Metabolic	DKA, sickle cell crisis, toxin, Addisonian crisis	Toxic ingestions (e.g. acetaminophen, iron, NSAIDs, etc.), lead poisoning, porphyria
Other	Significant trauma	Abdominal wall injury, herpes zoster, psychiatric, abscess, hernia, mesenteric adenitis

- differential can be focused anatomically by location of pain: right upper quadrant, left upper quadrant, right lower quadrant, left lower quadrant, epigastric, periumbilical, diffuse

History
- pain: OPQRST
- review symptoms from genitourinary, gynecological, gastrointestinal, respiratory, and cardiovascular systems
- abdominal trauma/surgeries, most recent colonoscopy, most recent endoscopy, last FOBT/FIT test

Physical Exam
- vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and cardiac exams as indicated by history

Investigations
- ABCs, do not delay management and consultation if patient unstable
- labs: CBC, electrolytes, glucose, BUN/Cr, U/A ± liver enzymes, LFTs, lipase, β-hCG, ECG, troponins, ± VBG/lactate
- AXR: if suspicious of foreign body or SBO (small bowel obstruction) in low resource setting. Can also use if frequent SBOs and usual conservative management
- CXR upright: look for pneumoperitoneum (free air under diaphragm), lung disease
- U/S: all gynecologic structure, testicles, biliary tract, ectopic pregnancy, appendicitis in children and young adults, nephro-/urolithiasis in young patients, AAA, free fluid; in select cases, can proceed to CT if U/S is non-diagnostic but there is high clinical suspicion
- CT: SBO, trauma, AAA, pancreatitis, nephro-/urolithiasis, appendicitis, and diverticulitis

Ruptured AAA
Flank/back pain
Pulsatile abdominal mass
Hypotension

Management
- NPO, IV, NG tube (if SBO), analgesics, consider antibiotics and anti-emetics
- growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: internal medicine, general surgery, vascular surgery, gynecology, etc.

Disposition
- admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develops

Acute Pelvic Pain

Etiology

- gynecological
  - ovaries: ruptured ovarian cysts (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass), mittelschmerz
  - fallopian tubes: salpingitis, tubal abscess, hydrosalpinx
  - uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in a pregnant patient (degeneration), PID, cervicitis
  - other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), endometriosis and dysmenorrhea, sexual or physical abuse, adrenal neoplasms
- non-gynecological (see causes of lower abdominal pain above)

History and Physical Exam

- pain: OPQRST
- associated symptoms: vaginal bleeding, discharge, dyspareunia, bowel and/or bladder symptoms
- pregnancy and sexual history, including oligo/amenorrhea, menorrhagia, and fibroids
- vitals
- gynecological exam: assess for cervical motion tenderness/"chandelier sign" (suggests PID)
- abdominal exam

Investigations

- β-hCG for all women of childbearing age
- CBC and differential, electrolytes, glucose, creatinine, BUN, culture and sensitivity, PTT/INR
- U/A to rule out urologic causes
- vaginal and cervical swabs for culture and sensitivity if performing a pelvic exam or urine NAAT for STI testing if no speculum exam is performed
- pelvic and abdominal U/S: evaluate adnexa, thickness of endometrium, pregnancy, free fluid or masses in the pelvis
- Doppler flow studies for ovarian torsion

Management

- general: analgesia, determine if admission and consults are needed
- specific:
  - ovarian cysts
    - unruptured or ruptured, and hemodynamically stable: analgesia and follow-up
    - ruptured with significant hemoperitoneum: may require surgery
  - ovarian torsion: surgical detorsion or removal of ovary
  - uncomplicated leiomyomas, endometriosis, and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  - PID: broad spectrum antibiotics (ceftriaxone 1 g IV q24 h, doxycycline 100 mg PO/IV q12 h, and metronidazole 500 mg PO/IV q12 h), recommend low threshold to treat empirically

Disposition

- referral: gynecological or obstetrical causes requiring surgical intervention, requiring admission, or oncological in nature
- admission: patients requiring surgery, IV antibiotics/pain management
- discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

Gynecological Causes of Pelvic Pain

- Ovarian cyst
- Dysmenorrhea
- Mittelschmerz
- Endometriosis
- Ovarian torsion
- Uterine fibroids/neoplasm
- Adnexal neoplasm
- PID + cervicitis

U/S is the preferred imaging modality in the assessment of acute pelvic pain

Possible Causes of Coma

AEIOU TIPS
Acidosis/**A**lcohol
Epilepsy
Infection
Oxygen (hypoxia)/**O**piates
Uremia
Temperature/**T**rauma (especially head)
Insulin (too little or too much)
Psychogenic/**P**oisoning
Structural or space-occupying lesion

Altered Level of Consciousness

Definitions

- altered mental status: collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness, including:
  - delirium (see Psychiatry, PS23)
  - dementia (see Psychiatry, PS24)
  - lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  - stupor: unresponsiveness but rousable
  - coma: a sleep-like state, not rousable to consciousness

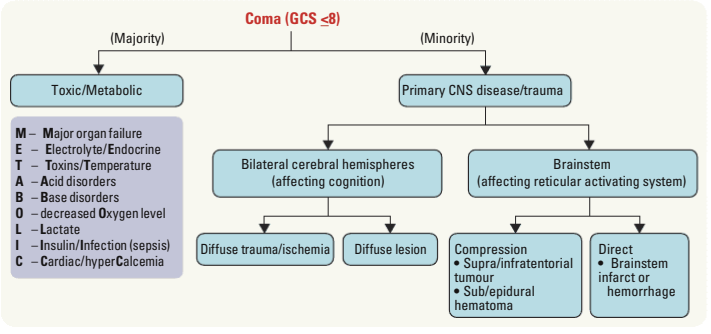


Figure 10. Etiology of coma

MANAGEMENT OF ALTERED LOC

History

- obtain collateral from family, friends, police, paramedics, patient record, MedicAlert® bracelet, etc.
- onset and progression
  - antecedent trauma, seizure activity, fever
  - abrupt onset suggests CNS hemorrhage/ischaemia, cardiac cause, or poisoning
  - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- determine patient's baseline LOC
- past medical history (e.g. similar episode(s), depression, overdose, changes to usual medications)

Physical Exam

- ABCs, vitals including temperature; cardiac, respiratory, abdominal exams
- complete neurological exam; in particular, examination of the eyes (pupils equal and reactive to light (PEARL))
- use the GCS to evaluate LOC (see *Patient Assessment/Management, ER2*)

Investigations

- blood work
  - serum glucose level, electrolytes, creatinine, BUN, LFTs, serum osmolality, CBC, VBG, lactate, PT/PTT/INR, troponins
  - serum acetaminophen, salicylate levels, ethanol (± toxic alcohols)
- imaging
  - CT head, CXR (if respiratory compromise or symptoms)
- other tests
  - ECG, U/A, urine toxicology

Diagnosis

- distinguish between structural and toxic-metabolic coma
  - structural coma
    - pupils, extraocular movements, and motor findings, if present, are usually asymmetric
    - look for focal or lateralizing abnormalities
  - toxic-metabolic coma
    - dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
    - respiratory depression with intact upper brainstem (e.g. equal and reactive pupils)
    - extraocular movements and motor findings are symmetric or absent
    - essential to re-examine frequently because status can change rapidly
- diagnosis may become apparent only with the passage of time
  - delayed deficit after head trauma suggestive of epidural hematoma (characteristic "lucid interval")

Table 13. Toxic-Metabolic Causes of Fixed Pupils

Dilated	Dilated to Normal	Constricted
Anoxia Anticholinergic agents (e.g. atropine, tricyclic antidepressants) Methanol Cocaine Opioid withdrawal Amphetamines Hallucinogens Serotonin syndrome (MAOI, SSRI)	Hypothermia Barbiturates Antipsychotics	Cholinergic agents (e.g. organophosphates) Opioids (e.g. heroin/fentanyl), except meperidine

Management
- administer appropriate universal antidotes (mnemonic DONT)
  - D50W (50 mL) if hypoglycemic on point-of-care test (POCT) capillary blood glucose
  - oxygen if needed
  - naloxone 0.4 mg, up to 10 mg IV if opiate overdose suspected
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished

Disposition
- admission: if ongoing decreased LOC, admit to service based on tentative diagnosis, or transfer patient if appropriate level of care not available
- discharge: readily reversible alteration of LOC; ensure adequate follow-up care

Chest Pain

Table 14. Differential Diagnosis for Chest Pain

	Emergent	Usually Less Emergent
CVS	MI, unstable angina, aortic dissection, cardiac tamponade, arrhythmia	Stable angina, pericarditis, myocarditis
Respirology	PE, tension pneumothorax	Pneumonia, pleural effusion, malignancy, non-tension pneumothorax
GI	Esophageal rupture, Mallory-Weiss tear, pneumomediastinum	Mallory-Weiss tear or esophageal rupture, pneumomediastinum, GERD, esophageal spasm
MSK		Rib fracture, costochondritis
Other		Herpes zoster, psychiatric/panic attack

History and Physical Exam
- OPQRST, previous episodes, and change in pattern
- cardiac risk factors (HTN, DM, dyslipidemia, smoking, FHx)
- inquire about any previous cardiac procedures, last stress test, last angiogram, and if they are currently followed by a cardiologist
- vitals, cardiac, respiratory, peripheral vascular, abdominal exams

Investigations
- ECG (most important): assess for STEMI (or those that may evolve to STEMI), always compare with previous; may be normal in up to 50% of PE and acute MI
- CBC, electrolytes, Cr, BUN, glucose, PTT/INR, cardiac biomarkers (troponin), D-Dimer if indicated
- CXR: compare with previous
- CT if indicated (e.g. aortic dissection, PE)

Management and Disposition
- ABCs, O2 (if needed), cardiac monitors, IV access
- treat underlying cause and involve consultants as necessary
- consider further observation/monitoring if unclear diagnosis or risk of dysrhythmia
- can refer to HEART score to risk stratify patients with chest pain
- discharge: patients with a low probability of life-threatening illness due to resolving symptoms and negative workup; arrange follow-up (e.g. rapid/acute cardiac clinic) and instruct to return if SOB or increased chest pain develops

Life-Threatening Causes of Chest Pain

PET MAP
PE
Esophageal rupture
Tamponade
MI/angina
Aortic dissection
Pneumothorax

Imaging is necessary for all suspected aortic dissections, regardless of BP

Classic Angina Characteristics
1. Retrosternal location
2. Provoked by exertion
3. Relieved by rest or nitroglycerin

Risk for Coronary Artery Disease
3/3 = "typical angina" - high-risk
2/3 = intermediate risk for women >50 yr, all men
1/3 = intermediate risk in men >40 yr, women >60 yr

HEART Score

H (History)	
Highly suspicious history	2 pts
Moderately suspicious history	1 pt
Slightly or non-suspicious history	0 pts
E (ECG)	
Acute ischaemia	2 pts
LBBB, RBBB, LVH, PM	1 pt
No signs of acute ischaemia	0 pts
A (Age)	
>65 yr	2 pts
ages 45-65	1 pt
<45 yr	0 pts
R (Risk factors)	
3 risk factors*, or history of atherosclerotic disease	2 pts
1 or 2 risk factors	1 pt
No risk factors known	0 pts
T (Troponin)	
troponin >42 ng/L	2 pts
troponin 15-42 ng/L	1 pt
troponin 14 ng/L	0 pts

* Risk factors: Diabetes mellitus, current or recent (<30 d) smoker, hypertension, hypercholesterolemia, and family history of coronary artery disease

0 to 3 points = low risk (0.6% to 1.7% risk of major adverse cardiac events); 4 to 6 points = intermediate risk (16.6% risk); 7 to 10 points = high risk (50.1% risk)

Table 15. Comparison of Chest Pain Diagnoses

	Classic History	Classic Findings	Diagnostic Investigations	Management and Disposition
Acute Coronary Syndrome	New or worsening pattern of retrosternal squeezing/ pressure pain, radiation to arm/neck, dyspnea, worsened by exercise, relieved by rest, N/V, syncope	New or worsened murmur, hypotension, diaphoresis, pulmonary edema	ECG: ischaemia (15-lead if hypotensive, AV node involvement, or inferior MI), serial troponin I (sensitive 6-8 h after onset), CXR	ABCs, Aspirin®, anticoagulation, and emergent cardiology consult to consider percutaneous intervention or thrombolytic
Pulmonary Embolism	Pleuritic chest pain (75%), dyspnea; risk factors for venous thromboembolism	Tachycardia, hypoxemia; evidence of DVT	Wells' criteria: D-dimer, CT pulmonary angiogram, ventilation-perfusion (V/Q) scan; leg Doppler, CXR	ABCs, anticoagulation; consider airway management and thrombolysis if massive PE (hypotension and cardiovascular collapse)
Acute Pericarditis	Viral prodrome, anterior precordial pain, pleuritic, relieved by sitting up and leaning forward	Friction rub	ECG: sinus tachycardia, diffuse ST elevation, PR depression in II, III, aVF, and V4-6; reciprocal PR elevation and ST depression in aVR ±V1; echocardiography	ABCs, rule out MI, high dose NSAIDs ± colchicine; consult if chronic/recurrent, large pericardial effusion, or non-viral cause (e.g. SLE, renal failure, requires surgery)
Pneumothorax	Trauma or spontaneous pleuritic chest pain often in tall, thin, young athlete	Hemithorax with decreased/absent breath sounds, hyper-resonance; deviated trachea and hemodynamic compromise (if tension pneumothorax)	Clinical diagnosis CXR: posteroanterior view, lateral, expiratory views – lung edge, loss of lung markings, tracheal shift; deep sulcus sign on supine view POCUS: Loss of lung slide, lack of comet tails, barcode sign, ± transition point	ABCs, needle to 2nd ICS at mid-clavicular line or 5th ICS in mid-axillary line if unstable; urgent surgical consult/thoracostomy 4th intercostal space and chest tube
Aortic Dissection	Sudden severe tearing retrosternal or midscapular pain ± focal pain/neurologic loss in extremities in context of HTN	HTN; systolic BP difference >20 mmHg or pulse deficit between arms; aortic regurgitant murmur	CT angiogram; CXR: wide mediastinum, left pleural effusion, indistinct aortic knob, >4 mm separation of intimal calcification from aortic shadow, 20% normal	ABCs, reduce BP and HR; classify type A (ascending aorta, urgent surgery) vs. B (not ascending aorta, medical) on CT angiogram and urgent consult
Cardiac Tamponade	Dyspnea, cold extremities, ± chest pain; often a recent cardiac intervention or symptoms of malignancy, connective tissue disease	Beck's triad - hypotension, elevated JVP, muffled heart sounds; tachycardia, pulsus paradoxus >10 mmHg	Clinical diagnosis/ POCUS to look for pericardial effusion CXR: may show cardiomegaly, evidence of trauma, ECG may show electrical alternans	ABCs, cardiac surgery or cardiology consult, pericardiocentesis if unstable, treat underlying cause
Esophageal Rupture	Sudden onset severe pain after endoscopy, forceful vomiting, labour, or convulsion, or in context of corrosive injury or cancer	Subcutaneous emphysema, findings consistent with sepsis	CXR: pleural effusion (75%), pneumomediastinum; CT or water soluble contrast esophagogram	ABCs, early antibiotics, resuscitation, thoracics consult, NPO, consider chest tube
Esophagitis or GERD	Frequent heartburn, acid reflux, dysphagia, relief with antacids	Oral thrush or ulcers (rare)	None acutely	ABCs, PPI medication, avoid EtOH, tobacco, trigger foods
Herpes Zoster	Abnormal skin sensation – itching/tingling/pain – preceding rash by 1-5 d	None if early; maculopapular rash (with dermatomal distribution) developing into vesicles and pustules that crust	Clinical diagnosis; direct immunofluorescence assay	ABCs, anti-virals (if < <48 h onset), analgesia ± steroids, dressing; r/o ocular involvement/refer if necessary
MSK	History of injury	Reproduction of symptoms with movement or palpation (not specific – present in 25% of MI)	MSK injury or fracture on x-rays	ABCs, NSAIDs, rest, orthopedics consultation for fractures
Anxiety	Symptoms of anxiety, depression, history of psychiatric disorder; may coexist with physical disease	Tachycardia, diaphoresis, tremor	Diagnosis of exclusion	ABCs, arrange social supports, rule out suicidality and consider psychiatry consult

ACS more likely to be atypical in females, diabetics, and >80 yr. Anginal equivalents include dyspnea, diaphoresis, fatigue, non-retrosternal pain

It is important to look for reciprocal changes in STEMI in order to differentiate from pericarditis (diffuse elevations)

Tracheal deviation is away from tension or towards non-tension pneumothorax

Does this Patient with Chest Pain have Acute Coronary Syndrome?: The Rational Clinical Examination Systematic Review
JAMA 2015;314:1955-1965
Purpose: To review accuracy of the initial history, physical examination, ECG, and risk scores incorporating these elements with the first cardiac-specific troponin.
Methods: Systematic review of prospective studies among patients admitted to the ED with symptoms suggesting ACS.
Results: Prior abnormal stress test (specificity 96%; LR 3.1, 95% CI 2.0-4.7), peripheral artery disease (specificity 97%; LR 2.7, 95% CI 1.5-4.8), and pain radiating to both arms (specificity 96%; LR 2.6, 95% CI 1.8-3.7) were most suggestive of ACS. The most suggestive ECG findings were ST-segment depression and any evidence of ischaemia. The History, ECG, Age, Risk Factors, Troponin (HEART) (LR 13, 95% CI 7-24) and the Thrombolysis in MI (TIMI) risk scores (LR 6.8, 95% CI, 5.2-8.9) were both predictive of ACS in the high-risk scores.
Conclusions: Among patients with suspected ACS presenting to the ED, the initial history, physical examination, and ECG alone did not confirm or exclude the diagnosis of ACS. Instead, the HEART or TIMI risk scores, which incorporate the first cardiac troponin, provided more diagnostic information.

Conservative vs. Interventional Treatment for Spontaneous Pneumothorax
NEJM 2020;382:405-415
Purpose: Determine whether conservative management is an acceptable alternative to interventional management for uncomplicated, moderate-to-large primary spontaneous pneumothorax.
Methods: Open-label, multicenter, noninferiority trial. Patients 14-50 yr were recruited with a first-known, unilateral, moderate-to-large primary spontaneous pneumothorax. Patients (n=316) were randomly assigned to immediate interventional management of the pneumothorax or a conservative observational approach and were followed for 12 mo. The primary outcome was lung re-expansion within 8 wk.
Results: Re-expansion within 8 wk occurred in 129 of 131 patients with interventional management and in 118 of 125 with conservative management (P=0.02, for noninferiority). Conservative management resulted in a lower risk of serious adverse events or pneumothorax recurrence than interventional management.
Conclusions: The trial provides modest evidence that conservative management of primary spontaneous pneumothorax was noninferior to interventional management, with a lower risk of serious adverse events.

Table 16. Common Life-Threatening ECG Changes

Pathology	ECG Findings
Dysrhythmia	
Torsades de pointes	Ventricular complexes in upward-pointing and downward-pointing continuum (160-250 bpm)
Ventricular tachycardia	3 or more consecutive premature ventricular beats (>100 bpm, QRS >120 ms)
Ventricular flutter	Smooth sine wave pattern of similar amplitude (>200 bpm)
Ventricular fibrillation	Erratic ECG tracing, no identifiable waves
Conduction	
2nd degree heart block (Mobitz Type II)	Constant PR interval, intermittently dropped P wave
3rd degree heart block	Prolonged QRS complex (>0.12 s) RSR' in V5 or V6 Total AV dissociation, but stable P-P and R-R intervals
Ischaemia	
STEMI	ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression)
Metabolic	
Hyperkalemia	Initially, tall T-waves Followed by PR prolongation, QRS widening, loss of P waves Finally, sinusoidal pattern and pulse electrical activity (PEA)/Vfib/Asystole
Hypokalemia	P wave flattening QRS complex widening and flattening U waves appear Flattened T waves
Digitalis Toxicity	Range of arrhythmias may present Supraventricular tachycardia Slow ventricular response Frequent premature ventricular contractions At risk for AV blocks and ventricular irritability
Syndromes	
Brugada	Three types of repolarization patterns in leads V1, V2, and V3 Type 1 ("Brugada sign"): coved ST segment elevation >2mm in >1 of V1-V3, followed by an inverted T wave; only type that is diagnostic Syndrome diagnosis if patient has Brugada sign and one of the following: family history of sudden cardiac death at age <45; arrhythmia related symptoms (e.g. syncope, seizures); or ventricular arrhythmias (VFib, polymorphic ventricular tachycardia) Susceptible to deadly dysrhythmias, including VFib
Wellens	Marked T wave inversion in V2 and V3 Left anterior descending coronary stenosis
Long QT syndrome	QT interval longer than ½ of cardiac cycle Predisposed to ventricular dysrhythmias

Diagnosis of Pulmonary Embolism with D-Dimer Adjusted to Clinical Probability
NEJM 2019;381:2125-2134
Purpose: Retrospective analyses suggest that PE is ruled out by a D-dimer level of <1000 ng/mL in patients with a low clinical pretest probability (C-PTP) and by a d-dimer level of <500 ng/mL in patients with a moderate C-PTP.
Methods: Prospective study in which PE was considered to be ruled out without further testing in 2017 outpatients with a low C-PTP and a d-dimer level of <1000 ng/mL or with a moderate C-PTP and a d-dimer level of <500 ng/mL. If PE was not diagnosed, patients did not receive anticoagulant therapy. Patients were followed for 3 mo for VTE.
Results: Of the 1325 patients who had a low C-PTP or moderate C-PTP and a negative d-dimer test, none had VTE during follow-up. This diagnostic strategy resulted in the use of chest imaging in 34.3% of patients. A strategy in which PE is considered to be ruled out with a low C-PTP and a d-dimer level of <500 ng/mL would result in the use of chest imaging in 51.9%.
Conclusion: A combination of a low C-PTP and a d-dimer level of <1000 ng/mL identified a group of patients at low-risk for PE during follow-up.

Headache

- see Neurology, N46

Etiology

- **common and less serious**
  - common migraine (without aura)/classic migraine (with aura)
    - common: unilateral, throbbing, aggravated by activity, moderate/severe intensity, N/V, photo-/phonophobia
    - classic: fully reversible aura symptoms that precede headache, e.g. flashing lights, pins and needles (paresthesia), loss of vision, dysarthria
    - treatment: simple analgesics (NSAIDs, acetaminophen, Aspirin®), antiemetics, triptans
    - family physician to consider prophylactic treatment
  - tension headache
    - bilateral, non-throbbing, not aggravated by routine physical activity, mild-moderate intensity
    - can last 30 min to 7 d
    - triggered with stress, sleep deprivation
    - treatment: modify stressor(s), simple analgesics (NSAIDs, acetaminophen, Aspirin®)
- **less common but potentially fatal**
  - subarachnoid hemorrhage (SAH) (see Neurosurgery, NS22)
    - sudden onset, "worst headache of life," maximum intensity within minutes, "thunderclap headache"
    - increased pain with exertion, N/V, meningeal signs
    - diagnosis
      - new generation CT 100% sensitive within 6 h of onset (hyperattenuating signal around Circle of Willis)
      - LP to look for xanthochromia if suspected SAH and normal CT after 6 h
    - management: urgent neurosurgery consult
  - increased ICP
    - worse in morning, when supine or bending down, with cough or Valsalva

Common Therapeutic Approach to Severe Migraine

1 L bolus of NS

Prochlorperazine/metoclopramide 10 mg IV

Ketorolac 30 mg IV

Dexamethasone 10 mg IV

Other options include haloperidol, metoclopramide, ergotamine, sumatriptan, analgesics

Ottawa SAH Rule
JAMA 2013;310(12):1248-1255
Use for alert patients older than 15 yr with new severe non-traumatic headache reaching maximum intensity within 1 h
Not for patients with new neurologic deficits, previous aneurysms, SAH, brain tumours, or history of recurrent headaches (≥3 episodes over the course of ≥6 mo)
Investigate if ≥1 high-risk variables present:
- Age ≥40 yr
- Neck pain or stiffness
- Witnessed loss of consciousness
- Onset during exertion
- Thunderclap headache (instantly peaking pain)
- Limited neck flexion on examination

Subarachnoid hemorrhage can be predicted with 100% sensitivity using this rule.

- physical exam: neurological deficits, cranial nerve palsies, papilledema
- diagnosis: CT head, LP if suspect idiopathic intracranial hypertension (risk of blindness if missed)
- management: consult neurosurgery

- meningitis (see Infectious Diseases, ID17)
  - at least two of the following features suggests that the headache could be due to meningitis: fever, neck stiffness, altered mental status
  - possible clinical/laboratory findings: nausea, focal neurologic signs, seizure, papilledema, petechial rash, high CSF WBC count, growth of organism in blood culture
  - investigations: rule out increased ICP (CT head, mental status normal, no neurological signs, no papilledema), if ruled out then perform diagnostic LP
  - treatment: early empiric antibiotics (high dose ceftriaxone + vancomycin ± ampicillin if >50 y/o or immunocompromised) ± acyclovir ± steroid therapy (administer based on clinical suspicion, DO NOT wait for LP)
- giant cell arteritis/temporal arteritis (causes significant morbidity, blindness) (see Ophthalmology, OP36)
  - vasculitis of large and mid-sized arteries, gender 3:1 F:M, most commonly ages >70
  - headache, scalp tenderness, jaw claudication, arthralgia, myalgia, fever, malaise, weight loss
  - temporal artery tender on palpation, RAPD, optic disc edema on fundoscopy
  - labs: elevated ESR, CRP
  - temporal artery biopsy is gold standard for diagnosis
  - associated with polymyalgia rheumatica
  - treatment: high-dose steroids immediately if suspected, no need to hold treatment until pathology results
- cerebral venous sinus thrombosis
  - physical symptoms depend heavily on location, size, and extent of the clot. They may include gradual or sudden onset headache, vomiting, papilledema, visual disturbances, focal neurological deficits, seizures, and acute mental status changes
  - investigations: neuroimaging (e.g. CT head, CT venography) to assess and r/o other acute processes (e.g. intracranial hemorrhage), CBC with coagulation studies and/or D-dimer, consider LP to r/o meningitis
  - treatment: anticoagulation (most commonly LMWH or heparin)

Disposition
- admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications
- discharge: assess for risk of narcotic misuse; most patients can be discharged with appropriate analgesia and follow-up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

Joint Pain

- see Rheumatology, RH3
- rule out life-threatening causes e.g. septic joint (see Orthopedic Surgery, OR11)

History and Physical Exam
- history: recent trauma, drug use (anticoagulants, glucocorticoids)
- associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
- patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
- inflammatory symptoms: morning stiffness ≥30 min, pain/stiffness that ease with activity, mid-day fatigue, soft tissue swelling
- non-inflammatory symptoms: morning stiffness <30 min, stiffness short-lived after inactivity, increasing pain with activity
- assess for pain with ROM, localized joint pain, effusion, erythema, warmth, swelling, inability to bear weight, fever; may indicate presence of septic joint

Investigations
- blood work: CBC, ESR, CRP, INR/PTT, blood cultures, urate
- joint x-ray ± contralateral joint for comparison
- bedside U/S to identify effusion ± joint aspiration
- test joint aspirate for: culture, WBC, polynuclear cells, glucose, Gram stain, crystals

Management
- septic joint: empiric IV antibiotics ± orthopedic consultation for joint decompression and drainage
- crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids
  - do not use allopurinol for acute flares, as it may worsen acute attack
- acute polyarthritis: NSAIDs, analgesics (acetaminophen ± opioids), local or systemic corticosteroids
- osteoarthritis: NSAIDs, acetaminophen
- soft tissue pain:
  - non-pharmacologic treatment: local heat or cold, electrical stimulation, massage
  - pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

Validation of the Ottawa Subarachnoid Hemorrhage Rule in Patients with Acute Headache
CMAJ 2017;189:E1379-E1385
Purpose: Validate the Ottawa SAH Rule in emergency department patients.
Methods: Prospective cohort study at 6 university-affiliated tertiary-care hospital emergency departments in Canada from 2010-2014. Included alert, neurologically intact adult patients with headache peaking within 1 hour of onset. The rule was scored before investigations.
Results: 1153/1743 potentially eligible patients were enrolled, 67 had subarachnoid hemorrhage. Ottawa SAH rule had 100% sensitivity and 13.6% specificity with similar neuroimaging rates (87%).
Conclusions: The Ottawa SAH Rule was sensitive for identifying subarachnoid hemorrhage in otherwise alert and neurologically intact patients.

Meningitis
Do not delay IV antibiotics for LP
Deliver first dose of dexamethasone with or before first dose of antibiotic therapy

Parenteral Dexamethasone for Preventing Recurrence of Acute Severe Migraine Headache
BMJ 2008;336(7657):1359
Purpose: To examine effectiveness of parenteral corticosteroids for relief of acute severe migraine headache and prevention of recurrent headaches.
Methods: Meta-analysis of RCTs comparing corticosteroids (alone or in combination with standard abortive therapy) to placebo or any other standard treatment for acute migraine in adults.
Results: Seven RCTs met eligibility criteria, all of which used standard abortive therapy and subsequently compared single dose parenteral dexamethasone to placebo. All trials examined pain relief and recurrence of headache within 72 hr. While dexamethasone and placebo were comparable for acute pain reduction (mean difference 0.37, 95% CI -0.20 to 0.94) and side effect profiles, dexamethasone provided lower recurrence rates (relative risk 0.75, 0.60 to 0.90; number needed to treat 9).
Conclusion: Single dose parenteral dexamethasone with standard abortive therapy is associated with a 26% relative reduction in headache recurrence within 72 h.

Back Pain

- see Family Medicine, FM11
- use Clinically Organized Relevant Exam (CORE) Back Tool to screen for common mechanical back pain syndromes
- rule out extraspinal emergencies: aortic dissection, AAA, PE, MI, retroperitoneal bleed, pancreatitis
- rule out spinal emergencies: osteomyelitis, cauda equina syndrome, epidural abscess or hematoma, discitis, spinal fracture, or malignancy

History and Physical Exam
- evaluate risk for fracture (osteoporosis, age, trauma), infection (IV drug user, recent spinal intervention, immunosuppression), cancer, vascular causes (cardiac risk factors), neurological symptoms (e.g. saddle anesthesia)
- typical musculoskeletal back pain is moderate, worse with movement or cough with no visceral symptoms
- assess vital signs, perform precordial, abdominal, and neurologic examination of lower extremities

Investigations
- U/A, post-void residual bladder scan
- reserve imaging for neurological deficits, metastases, and patients at high-risk of fracture, infection, cancer, or vascular cause
  - consider CT if trauma or fracture risk
  - urgent MRI if neurological findings

Management
- treat underlying cause
- lumbosacral strain and disc herniation: analgesia and continue daily activities as much as tolerated; discuss red flags and organize follow-up
- spinal infection: early IV antibiotics and infectious disease/spine surgery consultation
- cauda equina syndrome: dexamethasone, early spine surgery consultation

Red Flags for Back Pain

Bowel or bladder dysfunction
Anesthesia (saddle)
Constitutional symptoms
K - Chronic disease, Constant pain
Paresthesia
Age >50 and mild trauma
IV drug use/infection
Neuromotor deficits

Seizures

- see Neurology, N18

Definition
- paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons
- status epilepticus: continuous or intermittent seizure activity for greater than 5 min without regaining consciousness (life-threatening)

Categories
- generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
- partial seizure (focal): simple partial, complex partial
- causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP), metabolic disturbance (hypo-/hyperglycemia, hypo-/hypernatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
- differential diagnosis: syncope, stroke/TIA, psychogenic non-epileptic seizure, migraines, movement disorders, narcolepsy/cataplexy

History and Physical Exam
- history of seizures, identify potential precipitants (illness, alcohol withdrawal, sleep deprivation)
- preceding aura, rapid onset, brief duration, alterations in consciousness, tonic-clonic movements, and post-ictal symptoms would suggest a seizure
- common signs include tongue biting (high specificity), loss of bladder/bowel control, emesis, and aspiration
- perform vitals, complete neurologic examination, and look for injuries to head, spine, and shoulder (particularly posterior dislocations)

Minimum Workup in an Adult with 1st Time Seizure
CBC and differential
Electrolytes including Ca^{2+}, Mg^{2+}, PO_4^{3-}

If administering phenytoin, patient must be on a cardiac monitor as dysrhythmias and/or hypotension may occur

If IV access is not feasible, midazolam 0.2 mg/kg IM up to 10 mg can be used for initial control of seizure in adults

Table 17. Concurrent Investigation and Management of Status Epilepticus

Timing	Steps
Immediate	Protect airway with positioning; intubate if airway compromised or elevated ICP Monitor: vital signs, ECG, oximetry; POCT capillary blood glucose Establish IV/IO access Benzodiazepine - lorazepam 2 mg IV at 2 mg/min up to 10 mg or midazolam 5 mg IM up to 10 mg; repeat at 10 min if ineffective; intranasal if no IV/IO access Fluid resuscitation IV dextrose if glucose 33 mmol/L Give 50% glucose 50 mL (preceded by thiamine 100 mg IM if concerned about alcohol withdrawal) Obtain CBC, electrolytes, Ca $^{2+}$, Mg $^{2+}$, VBG, serum blood glucose, toxins, and antiepileptic drug levels; β-hCG Vasopressor support if sBP <90 or MAP <70 mmHg after aggressive fluid resuscitation
Urgent	Establish second IV line If status persists, phenytoin 20 mg/kg IV at 25-50 mg/min in adults; may give additional 10 mg/kg IV 10 min after loading infusion If seizure resolves, antiepileptic drug still required to prevent recurrence (levetiracetam: loading dose of 60 mg/kg IV in adults, maximum 4500 mg, infused over 5 to 15 min) EEG monitoring to evaluate for non-convulsive status epilepticus

Table 17. Concurrent Investigation and Management of Status Epilepticus

Timing	Steps
Refractory	If status persists after maximum doses above, consult ICU and start one or more of: Phenobarbital 20 mg/kg IV at 50 mg/min Midazolam 0.2 mg/kg IV loading dose and 0.1-0.4 mg/kg/h Propofol 2 mg/kg IV at 2-5 mg/kg/h then loading dose then 2-10 mg/kg/h Requires definitive airway management including rapid sequence intubation and assisted ventilation. Electroencephalography (EEG) for continuous monitoring
Post-Seizure	Investigate underlying cause: consider CT, LP, MRI, ICP monitoring

Note: All interventions should be done as soon as possible. Adapted from Brophy et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23

Disposition
- decision to admit or discharge should be based on the underlying disease process identified
  - if a patient had a brief generalized seizure and has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
- first-time seizure patients being discharged should be referred to a neurologist for follow-up
- admitted patients should generally have a neurology consult
- patient should not drive until medically cleared (local regulations vary)
  - complete notification form to appropriate authority regarding ability to drive (based on local legal requirements)
- warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)

Intramuscular vs. Intravenous Therapy for Prehospital Status Epilepticus
NEJM 2012;366:591-600
Purpose: To investigate the efficacy of intramuscular (IM) midazolam with that of IV lorazepam for children and adults in status epilepticus treated by paramedics.
Methods: Double-blind, randomized, non-inferiority trial. Subjects whose convulsions had persisted more than 5 min and were still convulsing after paramedics arrived were given the study medication by either IM or IV infusion. Primary outcome: absence of seizures at the time of arrival in the emergency department without the need for rescue therapy.
Results: Seizures were absent without rescue therapy in 73% of the IM-midazolam group and in 63.4% of the IV-lorazepam group (P<0.001 for noninferiority and superiority). The median times to active treatment were 1.2 min in the IM midazolam group and 4.8 min in the IV-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 min and 1.6 min. Adverse-event rates were similar.
Conclusions: For subjects in status epilepticus, IM midazolam is at least as safe and effective as IV lorazepam for prehospital seizure cessation.

Shortness of Breath

- see Respirology, R3 and Cardiology and Cardiac Surgery, C6

Table 18. Differential Diagnosis for Dyspnea

	High Mortality/Morbidity	Usually Less Emergent
Respiratory	Airway obstruction (foreign body, epiglottitis, abscess, anaphylaxis) Pneumo/hemothorax Gas exchange (pulmonary edema, PE, pneumonia, acute exacerbations of asthma, or COPD)	Chronic obstructive, interstitial or restrictive lung disease Pleural effusion
Cardiac	CHF, MI, valvular disease, tamponade, arrhythmia	Chronic CHF, angina
Metabolic	Metabolic acidosis NYD, toxin ingestion	Anemia, hemoglobinopathy
Neuromuscular	Myasthenia gravis, diaphragmatic paralysis	CNS lesion, primary muscle weakness
Other	Deconditioning, respiratory splinting due to unrelated pain	Anxiety

History and Physical Exam
- acute SOB is often due to a relatively limited number of conditions; associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischaemia
  - fever, cough, and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
  - environmental or occupational exposures
- dyspnea may be the sole complaint and the physical exam may reveal few abnormalities (e.g. PE, pneumothorax)
- vitals including pulse oximetry
  - wheeze and stridor (ventilatory) vs. crackles (parenchymal), JVP, and murmurs

Investigations
- blood work
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider ABG/VBG
  - serial cardiac enzymes and ECG if considering cardiac source
  - PERC or Wells scores to consider appropriateness of D-dimer
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection, or interstitial fluid)
  - CT chest may be indicated in acute dyspnea, specifically when suspicion for thromboembolic disease (i.e. PE)

Disposition
- history and physical exam lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified and its severity
  - non-invasive positive pressure ventilation (NIPPV) should be considered in patients with severe COPD or CHF, may reduce the need for intubation in this patient population
  - consider intubation in COPD and CHF if NIPPV will not be tolerated (e.g. decreased LOC, vomiting)
- if discharging, organize follow-up and educate regarding signs to return to hospital

Syncope

Definition
- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system (brainstem) hypoperfusion

Etiology
- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, orthostatic, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)

History
- gather details from witnesses, and clarify patient's experience (e.g. dizziness, ataxia, or true syncope)
  - two key historical features: prodrome and situation (setting, patient posture)
- distinguish between syncope and seizure (see Neurology, N18)
  - some patients may have myoclonic jerks with syncope – NOT a seizure
    - signs and symptoms during presyncope, syncope, and postsyncope (seizure has post-ictal period afterwards, syncope does not)
    - past medical history, drugs
    - think anatomically in differential: pump (heart), blood, vessels, brain
- syncope is cardiogenic until proven otherwise if
  - there is sudden loss of consciousness with no warning or prodrome
  - syncope is accompanied by chest pain

Physical Exam
- postural BP and HR
- cardiac, respiratory, and neurological exams
- examine for signs of secondary injury caused by syncopal episode (e.g. head injury)

Investigations
- ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval, Brugada Syndrome, right ventricular strain, hypertrophic cardiomyopathy)
- POCT capillary blood glucose
- consider blood work: CBC, electrolytes, BUN/Cr, VBG, troponin, Ca^{2+}, Mg^{2+}, β-hCG, D-dimer
- consider toxicology screen

Management
- ABCs, IV, O_2, monitor
- cardiogenic syncope: admit to medicine/cardiology
- low-risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

Disposition
- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow up with family physician
  - educate about avoiding orthostatic or situational syncope
  - evaluate the patient for fitness to drive or work
  - patients with recurrent syncope should avoid high-risk activities (e.g. driving)

Sexual Assault

Epidemiology
- 1 in 5 women and 1 in 50 men will be sexually assaulted in their lifetime; only 7% are reported

General Approach
- ABCs, treat acute, serious injuries; physician priority is to treat medical issues and provide clearance
- ensure patient is not left alone and provide ongoing emotional support
- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained); ideally by an experienced provider (generally a sexual assault nurse examiner)
- administer Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault; ideally by an experienced provider
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests or if <16 y/o (i.e. legally required)

Interprofessional teams are key; many centres or regions have sexual assault teams who specialize in the assessment and treatment of sexual assault victims, leaving emergency physicians responsible only for significant injuries and medical clearance

History
- ensure privacy for the patient – others should be asked to leave
- questions to ask: who, when, where did penetration occur, what happened, any weapons, or physical assault?

- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
  - gravidity, parity, last menstrual period
  - contraception use
  - last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

Physical Exam
- never re-traumatize a patient with the examination
- intimate exams and specimen collection should ideally be deferred to a sexual assault nurse if there is one available. This is to avoid re-traumatization and for medico-legal reasons (samples once collected must be secured, otherwise their validity will be questioned during legal proceedings)
- general examination
  - mental status
  - sexual maturity
  - patient should remove clothes and place in paper bag
  - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
- pelvic exam and specimen collection
  - ideally before urination or defecation
  - examine for seminal stains, hymen, signs of trauma
  - collect moistened swabs of dried seminal stains
  - pubic hair combings and cuttings
  - speculum exam
    - lubricate with water only
    - vaginal lacerations, foreign bodies
    - Pap smear, oral/cervical/rectal culture for gonorrhea and chlamydia
    - posterior fornix secretions if present or aspiration of saline irrigation
    - immediate wet smear for motile sperm
    - air-dried slides for immotile sperm, acid phosphatase, ABO group
- fingernail scrapings and saliva sample from victim

Investigations
- Venereal Disease Research Lab (VDRL): repeat in 3 mo if negative
- serum β-hCG
- blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

Management
- involve local/regional sexual assault team (sexual assault forensic examiner or sexual assault nurse examiner)
- medical
  - suture lacerations, tetanus prophylaxis
  - gynecology consult for foreign body, complex lacerations
  - assume positive for gonorrhea and chlamydia
    - management: ceftriaxone IM x 1 dose (500 mg <150 kg; 1g >150 kg) and doxycycline 100 mg PO BID x 7 d (alt: azithromycin 1 g PO x 1 dose)
  - may start post-exposure prophylaxis for hepatitis B, syphilis, HIV
  - pre and post counselling for HIV testing
  - pregnancy prophylaxis offered
    - levonorgestrel 1.5 g PO STAT (Plan B®)
- psychological
  - high incidence of psychological sequelae
  - have victim change and shower after exam completed

Disposition
- discharge if injuries/social situation permit
- follow-up with physician in rape crisis center within 24 h for repeat pregnancy and STI testing
- best if patient does not leave ED alone

INTIMATE PARTNER VIOLENCE
- women are usually the victims, but male victimization also occurs
- identify the problem (need high index of suspicion)
  - suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns, or other injuries; often inconsistent with history provided)
  - somatic symptoms (chronic and vague complaints)
  - psychosocial symptoms
  - clinician impression (your 'gut feeling' e.g. overbearing partner that won't leave patient's side)
- if disclosed, be supportive and assess danger
- patient must consent to follow-up investigation/reporting (unless patient is <16 y/o)

Management
- treat injuries and document findings
- ask about sexual assault and children at home (encourage notification of police)
- safety plan with good follow-up with family physician/social worker

Medical Emergencies

Anaphylaxis and Allergic Reactions

Etiology

- anaphylaxis is an exaggerated immune-mediated hypersensitivity reaction that leads to systemic histamine and vasoactive mediator release leading to increased vascular permeability and vasodilation
- regardless of the etiology, the presentation and management of anaphylactic reactions are the same
  - epinephrine (1:1000) 0.3-0.5 mg (IM in anterolateral thigh)
- allergic (e.g. re-exposure to allergen)
- non-allergic (e.g. exercise-induced)

Most Common Triggers for Anaphylaxis
Foods (nuts, shellfish, etc.)
Stings
Drugs (penicillin, NSAIDs, ACEI)
Radiographic contrast media
Blood products
Latex

Diagnostic Criteria

- diagnosis of anaphylaxis is highly likely with any of the following:
  1. acute onset of an illness (min to h) with involvement of the skin, mucosal tissue, and at least one of
     - respiratory compromise (e.g. dyspnea, wheeze, stridor, hypoxemia)
     - hypotension/end-organ dysfunction (e.g. hypotonia, collapse, syncope, incontinence)
  2. two or more of the following after exposure to a LIKELY allergen for that patient (min to h)
     - involvement of the skin-mucosal tissue
     - respiratory compromise
     - hypotension or associated symptoms
     - persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
  3. hypotension after exposure to a KNOWN allergen for that patient (min to h)
     - management is also appropriate in cases which do not fulfill criteria, but who have had previous episodes of anaphylaxis
     - life-threatening differentials for anaphylaxis include asthma and septic shock
     - angioedema may mimic anaphylaxis but tends not to improve with standard anaphylaxis treatment

Anaphylaxis should be suspected if airway, breathing, or especially circulation compromise is present after exposure to a known allergen

Hypotension is defined as sBP >30% decrease from baseline or
≥11 yr: <90 mmHg
1-10 yr: <70 mmHg + (2 x age)
1 mo-1 yr: <70 mmHg

Management

- moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
  - epinephrine (1:1000) 0.3-0.5 mg (IM in anterolateral thigh)
  - antihistamine: cetirizine 10 mg PO/IV
  - salbutamol (Ventolin®) 1 cc via MDI
- severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
  - ABCs, may need definitive airway (e.g. ETT) due to airway edema
  - epinephrine (1:1000) 1-10 µg/min IV (or via ETT if no IV access) titrated to desired effect
  - antihistamine: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg) or cetirizine (Reactine®) 10 mg IV
  - glucocorticoids: methylprednisolone 125-250 mg IV or prednisone/prednisolone 40-60 mg PO
  - large volumes of crystalloid may be required
  - try to remove trigger (e.g. search for insect stingers, decompress GI tract if possible)
- patients on β-blockers may not respond to epinephrine in an anaphylactic reaction and may benefit from glucagon for reversal

Early epinephrine is lifesaving and there are no absolute contraindications

Disposition

- all patients should be kept under observation until symptoms fully resolve, especially if severe anaphylaxis and/or those who needed >1 dose of epinephrine; arrange follow-up with family physician in 24-48 h
- can have second phase (biphasic) reaction up to 72 h later, patient may need to be supervised
- educate patient on avoidance of allergens
- instructions to seek immediate medical attention in ED during any future anaphylaxis reaction, even when self-treatment has been self-initiated
- medications
  - epinephrine auto-injector
  - H1 antagonist (cetirizine 10 mg PO once daily)
  - Second-generation H1 antagonists (e.g. cetirizine) are less sedating than first-generation H1 antagonists (e.g. Benadryl®)
  - glucocorticoids not recommended

Pediatric Dosing
Epinephrine: 0.01 mg/kg IM up to 0.5 mg q5-10 min
Initial crystalloid bolus: 20-30 mL/kg, reassess
Epinephrine infusion: 0.1-1.5 µg/kg/min
Diphenhydramine: 1 mg/kg PO/IV q4-6 h
Methylprednisolone: 1-2 mg/kg IV

Asthma

- see Respirology, R7 and Pediatrics, P91
- chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction

History and Physical

- find cause(s) of asthma exacerbation (e.g. viral, environmental, etc.)
- history of asthma control; severity of exacerbations (e.g. ICU, intubation history)
- signs of respiratory distress (e.g. accessory muscle use)
- vitals, specifically O_2 saturation

Beware of the silent chest in asthma exacerbations. This is a medical emergency and requires aggressive treatment. Intubation of patients with severe asthma is extremely high risk and maximum medical therapy should be used to avoid it if possible

Investigations
- peak flow meter
- ± ABG if in severe respiratory distress
- CXR if diagnosis is uncertain to rule out pneumonia, pneumothorax, etc.

Table 19. Asthma Assessment and Management

Classifications	History and Physical Exam	Management
Respiratory Arrest Imminent	Exhausted, confused, diaphoretic, cyanotic Silent chest, ineffective respiratory effort Decreased HR, respiratory rate (RR) >30, pCO_2 >45 mmHg O_2 sat <90% despite supplemental O_2	Anticipate need for intubation (high risk for complications; ideally carried out by an experienced provider) 100% O_2, cardiac monitor, IV access Intubate (consider induction with ketamine) Short acting β-agonist (salbutamol): nebulizer 5 mg continually Short-acting anticholinergic (ipratropium): nebulizer 0.5 mg x 3 IV steroids: methylprednisolone 125 mg, salbutamol 1-2 mg/kg. IV epinephrine can be helpful, especially if associated hypotension
Severe Asthma	Agitated, diaphoretic, laboured respirations Speaking in words No relief from β-agonist O_2 sat <90%, FEV_1 <50%	Magnesium sulphate 2 g IV (25-50 mg/kg) O_2 to achieve O_2 sat >92% Short acting β-agonist (salbutamol): nebulizer 5 mg continually Short-acting anticholinergic (ipratropium): nebulizer 0.5 mg x 3 if not already given IV steroids: methylprednisolone 125 mg or 1-2 mg/kg
Moderate Asthma	SOB at rest, cough, congestion, chest tightness Speaking in phrases Inadequate relief from β-agonist FEV_1 50-80%	O_2 to achieve O_2 sat >92% Short-acting β-agonist (salbutamol): MDI or nebulizer q5 min Short-acting Anticholinergic (ipratropium): MDI or nebulizer x 3 Steroids: prednisone 40-60 mg PO
Mild Asthma	Exertional SOB/cough with some nocturnal symptoms Difficulty finishing sentences FEV_1 >80%	β-agonist Monitor FEV_1 Consider steroids (MDI or PO)

Disposition
- discharge is safe in patients with FEV1 or peak expiratory flow (PEF) >60% predicted, and may be safe if FEV_1 or PEF 40-60% predicted based on the patient's risk factors for recurrence of severe attack
  - risk factors for recurrence: frequent ED visits, frequent hospitalizations, recent steroid use, recent exacerbation, poor medication compliance, prolonged use of high dose β-agonists
- β-agonist MDI with aerochamber 2-4 puffs q2-4 h until symptoms controlled, then PRN
- initiate inhaled corticosteroids with aerochamber if not already prescribed
- if moderate to severe attack, administer prednisone 30-60 mg/d for 5-10 d with no taper
- counsel on medication adherence and educate on use of aerochamber
  - follow up with primary care physician or asthma specialist

Cardiac Dysrhythmias

- see Cardiology and Cardiac Surgery, C19

Bradydysrhythmias and AV Conduction Blocks
- AV conduction blocks
  - 1st degree: prolonged PR interval (>200 msec), no treatment required
  - 2nd degree
    - Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - Mobitz II: PR interval constant with dropped QRS complex, can progress to 3rd degree AV block
  - 3rd degree: P wave unrelated to QRS complex, PP and RR intervals constant
    - atropine and transcutaneous/transvenous pacing (atropine with caution)
    - if transcutaneous/transvenous pacing fails consider IV dopamine, epinephrine
  - long-term treatment for Mobitz II and 3rd degree block – internal pacemaker
- sinus bradycardia (rate <60 bpm)
  - can be normal (especially in athletes)
  - causes: vagal stimulation, vomiting, MI/ischemia, increased ICP, sinus node dysfunction, hypothyroidism, drugs (e.g. β-blockers, calcium channel blockers)
  - look for up-right P waves in lead II and/or biphasic in lead V1 – confirms sinus P wave origin
  - treat if symptomatic (hypotension, chest pain)
    - acute: atropine ± transcutaneous/transvenous pacing
    - sick sinus: transcutaneous/transvenous pacing
    - drug induced: discontinue/reduce offending drug, consider antidotes, pacing often ineffective, use IV epinephrine to increase chronotropy

Supraventricular Tachydysrhythmias (narrow QRS)
- sinus tachycardia (rate >100 bpm)
  - causes: increased sympathetic tone, drugs, fever, shock, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause
- regular rhythm (i.e. not sinus tachycardia)
  - vagal maneuvers (e.g. carotid massage, Valsalva)
  - continuous 12-lead ECG helpful during maneuvers or cardioversion if 1st episode; will help to elicit underlying etiology
  - adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once; warn patients regarding side effects (e.g. chest pain, nausea)

Elements of Well-Controlled Asthma
Can Respir J 2010;17(1):15-24
- Daytime symptoms <4x/wk
- Nocturnal symptoms <1x/wk
- No limitation in activity
- No absence from work/school
- Rescue inhaler use <4x/wk
- FEV_1 <90% personal best
- PEF <10-15% diurnal variation
- Mild infrequent exacerbations

Combined Inhaled β-Agonist and Anticholinergic Agents for Emergency Management in Adults with Asthma
Cochrane DB Syst Rev 2017:CD001284
Purpose: Determine the effectiveness of combined short-acting β-agonist (SABA) + short-acting anticholinergic (SAAC) vs. SABA alone to reduce hospitalization in adult patients presenting to the ED with an exacerbation of asthma.
Methods: Systematic review of RCTs.
Results: 23 trials, 2724 patients. Combination inhaled therapy was associated with reduced likelihood of hospitalization (RR 0.72, 95% CI 0.59-0.87) for severe but not mild or moderate asthma exacerbations. Combination therapy was also associated with improved FEV_1 (MD 0.25L, 95% CI 0.02-0.48) and PEF (MD 24.88, 95% CI 14.83-34.93) and patients were less likely to return to ED for additional care (RR 0.80, 95% CI 0.66-0.98). In contrast, patients receiving combination therapy were more likely to experience adverse events than those treated with SABA alone (OR 2.03, 95% CI 1.28-3.20).
Conclusions: Combination SAAC + SABA therapy reduces hospitalizations and improves pulmonary function in adults presenting to the ED with acute asthma. However, adults receiving combination therapy were more likely to experience adverse events, such as tremor, agitation, and palpitations, compared to patients receiving SABA alone.

Adenosine vs. Intravenous Calcium Channel Antagonists for Supraventricular Tachycardia
Cochrane DB Syst Rev 2017;CD005154
Purpose: Compare adenosine vs. calcium channel antagonists in terminating supraventricular tachycardia.
Methods: Systematic review of RCTs for any patient presenting with supraventricular tachycardia.
Results: 7 RCTs, 622 participants. Moderate-quality evidence shows no differences in the number or people reverting to sinus rhythm who were treated with adenosine or calcium channel antagonist (89.7% vs. 92.9%, OR 1.51). Low-quality evidence suggests no differences in major adverse event rates.
Conclusions: Moderate-quality evidence shows no differences in effects of adenosine and calcium channel antagonists for treatment of supraventricular tachycardia on reverting to sinus rhythm, and low-quality evidence suggests no differences in the incidence of hypotension.

In patients with a regular rhythm and a supraventricular tachydysrhythmia, a modified valsalva maneuver is effective in up to 43% of patients. Procedure: position the patient in a semi-recumbent position (45°). Instruct the patient to blow into the tip of a 10 cc syringe for 15 s. The patient should be targeting a pressure reading on the manometer of 40 mmHg, or blowing hard enough to move the plunger tip. Lower the patient flat, and passively raise their legs to a 45° angle for 15 s. Return the patient to a semi-recumbent position for an additional 45 s.

- electrical cardioversion if vagal maneuvers and adenosine unsuccessful
- rhythm converts: probable reentrant tachycardia (atrioventricular (AV) nodal reentrant tachycardia (AVNRT) more common than AV reentrant tachycardia (AVRT))
  - monitor for recurrence
  - treat recurrence with adenosine or longer acting medications
- rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
  - rate control (diltiazem, β-blockers) or rhythm control with cardioversion
  - consult cardiology if refractory

• irregular rhythm
- probable AFib, atrial flutter, or multifocal atrial tachycardia
- rate control (e.g. diltiazem, β-blockers), or rhythm control if AFib/flutter and at least <48 h from onset

Atrial Fibrillation

• most common sustained dysrhythmia; no organized P waves (atrial rate >300/min), irregularly irregular heart rate, narrow QRS (typically)
• etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, sinus node dysfunction
• treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
• decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
• acute management
- consider whether AFib is primary cause of symptoms; if different underlying cause, treat underlying cause first
- if unstable: immediate synchronized cardioversion
- hemodynamically stable patients with AFib <48 h: rhythm or rate control ± electrical or chemical cardioversion
- do not cardiovert if any of the following are present: valvular AFib (any duration) or non-valvular AFib (duration <12 h and recent stroke/TIA; duration 12-48 h and CHADS2 ≥2; or duration >48 h). Instead, start patient on appropriate anticoagulation and/or arrange for transesophageal echocardiogram to exclude a thrombus in the left atrial appendage

• electrical cardioversion: synchronized cardioversion
• chemical cardioversion: procainamide, flecainide, propafenone
• long-term management: rate or rhythm control, consider anticoagulation (see Cardiology and Cardiac Surgery, *CHADS2 score*, C22)

Ventricular Tachydysrhythmias (wide QRS)

• VTach (rate usually 140-200 bpm)
- definition: 3 or more consecutive ventricular beats at >100 bpm
- etiology: CAD with MI is the most common cause
- treatment: sustained VTach (>30 s) is an emergency
  - hemodynamic compromise: synchronized DC cardioversion
  - no hemodynamic compromise: synchronized DC cardioversion, amiodarone, procainamide

• VFib: call a code blue, follow ACLS for pulseless arrest
• torsades de pointes
- looks like VTach but QRS 'rotates around baseline' with changing axis and amplitude (twisted ribbon)
- etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
- treatment
  - IV Mg^{2+}, temporary overdrive pacing, isoproterenol
  - correct cause of prolonged QT

Acute Exacerbation of COPD

• see Respirology, R8
• progressive development of irreversible airway obstruction, typically caused by smoking

History and Physical Exam

• cardinal symptoms of acute exacerbation of COPD (AECOPD): increased dyspnea, increased coughing frequency or severity, increased sputum volume or purulence
• triggers: virus, pneumonia, PE, CHF, MI, drugs
• characterize previous episodes and hospitalizations, smoking history
• vital signs, LOC, signs of respiratory distress, respiratory exam

Investigations

• CBC, electrolytes, CXR, ECG, consider VBG
• Pulmonary Function Tests are NOT useful in managing acute exacerbations

Management

• oxygen: keep O_2 saturation 88-92% (be aware of chronic hypercapnic/CO_2 retainers but do not withhold O_2 if hypoxic)
• bronchodilators: short-acting β-agonist (salbutamol 4-8 puffs via MDI with spacer q15 min x3 PRN) ± short-acting anticholinergic (ipratropium 0.5 mg via MDI q30 min x3 PRN)
• steroids: prednisone 40-60 mg PO for 7-14 d, or methylprednisolone 1-2 mg/kg IV if severe exacerbation, or unable to take PO
• antibiotics: trimethoprim/sulfamethoxazole, cephalosporins, respiratory quinolones (given if all 3 cardinal symptoms present or 2 cardinal symptoms with increased sputum purulence or mechanical

If a patient with tachydysrhythmia is unstable, perform immediate synchronized cardioversion

If patient has Wolff-Parkinson-White and is in AFib, use procainamide or cardiovert; avoid AV nodal blocking agents (adenosine, digoxin, diltiazem, verapamil, β-blockers), as these can increase conduction through bypass tract, leading to cardiac arrest

Causes of Atrial Fibrillation

C ("sea") PIRATES
CHF, **C**ardiomyopathy
Pulmonary embolism
Ischaemic heart disease
Rheumatic or valvular disease
Anemia
Thyroid (hyperthyroidism)
EtOH, **E**levated blood pressure
Sick **S**inus, **S**tress - surgery, sepsis

Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation
NEJM 2019;380:1499-1508
Purpose: Patients with recent-onset AFib commonly undergo immediate restoration of sinus rhythm by cardioversion. Whether this is necessary is not known, since AFib often terminates spontaneously.
Methods: Randomly assigned patients with stable, recent-onset (<36 h), symptomatic AFib in the ED to be treated with a wait-and-see approach (delayed-cardioversion group) or early cardioversion. The wait-and-see approach involved initial treatment with rate-control medication only and delayed cardioversion if the AFib did not resolve within 48 h.
Primary endpoint: presence of sinus rhythm at 4 wk.
Results: The presence of sinus rhythm at 4 wk occurred in 91% of patients in the delayed-cardioversion group and in 94% in the early-cardioversion group (P=0.005 for noninferiority). Among the patients who completed remote monitoring during 4 wk of follow-up, a recurrence of AFib occurred in 30% of the delayed-cardioversion group and in 29% of the early-cardioversion group.
Conclusions: Wait-and-see approach was non-inferior to early cardioversion in stable AFib patients.

Physical Exam Findings in COPD
- Wheeze
- Maximum laryngeal height ≤4 cm
- Forced expiratory time ≥6 s
- Decreased breath sounds
- Decreased cardiac dullness

Need to Rule Out with COPD
- Exacerbation
- Pneumothorax
- CHF exacerbation
- Acute MI
- Pneumonia and other infectious causes
- PE

ventilation); no antibiotics for mild exacerbation (only 1 of 3 cardinal symptoms)
- ventilation: apply noninvasive positive-pressure ventilation (CPAP or Bi-PAP) if severe distress or signs of fatigue, arterial pH <7.35, or hypercapnic
- if life-threatening, intubate in ED and refer to ICU admission for ventilation (chance of ventilation dependency)

Disposition
- no specific guidelines for admission consider admission if: inadequate response to management, onset of new signs (cyanosis, altered LOC, peripheral edema, respiratory distress), marked increase in symptom intensity with increased oxygen requirement, hemodynamic instability
- lower threshold to admit if comorbid illness (e.g. diabetes, CHF, CAD, alcohol use disorder)
- if discharging, use antibiotics, taper steroids, up to 4-6 puffs QID of ipratropium and salbutamol, and organize follow-up

Heart Failure

- see Cardiology and Cardiac Surgery, C40

Etiology
- causes of chronic heart failure: decreased myocardial contractility (ischaemia, infarction, cardiomyopathy, myocarditis), pressure overload states (HTN, valve abnormalities, congenital heart disease), restricted cardiac output (myocardial infiltrative disease, cardiac tamponade)
- precipitants of acute decompensated heart failure (ADHF)
  - cardiac (ischaemia, infarction, arrhythmia, e.g. AFib)
  - medications (β-blockers, calcium channel blockers, NSAIDs, steroids, non-compliance)
  - dietary (increased sodium and/or water intake)
  - high output (anemia, infection, pregnancy, hyperthyroid)
  - other (renal failure, hypertensive crisis, iatrogenic fluid overload - blood transfusions or IV fluids)

Presentation
- left-sided heart failure
  - dyspnea, SOB on exertion, orthopnea, paroxysmal nocturnal dyspnea, nocturia, fatigue, altered mental status, presyncope/syncope, angina, systemic hypotension
  - hypoxia, decreased air entry to lungs, crackles, S3 or S4, pulmonary edema (on CXR), pleural effusion (usually right-sided)
- right-sided heart failure
  - dependent bilateral pitting edema, JVP elevation and positive abdominojugular test, ascites, hepatomegaly
- patients often present with a combination of right-sided and left-sided symptoms

Investigations
- blood work: CBC, electrolytes, AST, ALT, bilirubin, Cr, BUN, cardiac enzymes, brain natriuretic peptide
- CXR: most useful test (see sidebar)
- ECG: look for MI, ischaemia (ST elevation/depression, T-wave inversion), LVH, atrial enlargement, conduction abnormalities
- bedside ultrasound: Kerley B lines, pleural effusion, rule out cardiac tamponade
- echocardiogram: left ventricular function, structural heart disease
- rule out other serious diagnoses: PE, pneumothorax, pneumonia/empyema
- can be difficult to differentiate ADHF and AECOPD in patients who have both Kerley B lines, pleural effusion, elevated BNP

Management
- ABCs, may require intubation (rare with non-invasive ventilation, but consider if severe hypoxia)
- sit upright, cardiac monitoring, and continuous pulse oximetry
- saline lock IV, Foley catheter or an in out catheter
- 100% O_2 by mask
  - if poor response, may require Bi-PAP (preferred) or intubation (rare)
- medical
  - diuretic (if volume overloaded): furosemide 0.5-1 mg/kg IV, titrate to response
  - vasodilators (if sBP >100 mmHg): nitroglycerin 0.4 mg SL q5 min PRN
  - inotropes/vasopressors (if sBP <90 mmHg): first-line agent is norepinephrine; add dobutamine or epinephrine; milrinone helpful in refractory cases, but rarely available
- treat precipitating factor - e.g. rate control (β-blocker, calcium channel blockers) or rhythm-control (electrical or chemical cardioversion) if new AFib
- cardiology or medicine consult

Venous Thromboembolism

- see Respirology, R20

Risk Factors
- Virchow's triad: alterations in blood flow (venous stasis), injury to endothelium (smoking, HTN, surgery, catheter, trauma), hypercoagulable state (including pregnancy, use of oral contraceptive pills, malignancy)
- clinical risk factors (see *sidebar, Risk Factors for VTE, ER33*)

Precipitants of CHF Exacerbation

FAILURE
Forgot medication
Arrhythmia (Dysrhythmia)/Anemia
Ischaemia/Infarction/Infection
Lifestyle (e.g. high salt intake)
Upregulation of cardiac output (e.g. pregnancy, hyperthyroidism)
Renal failure
Embolism (pulmonary)

CHF on CXR
- Pulmonary vascular redistribution
- Perihilar infiltrates
- Interstitial edema, Kerley B lines
- Alveolar edema, bilateral infiltrates
- May see cardiomegaly, pleural effusions
- Peribronchial cuffing
- Fissural thickening (fluid in fissure)

Acute Treatment of CHF

LMNOP
Lasix® (furosemide)
Morphine
Nitroglycerin
Oxygen
Position (sit upright), Pressure (Bi-PAP)

Hospital Management Required if
- Acute MI
- Pulmonary edema or severe respiratory distress
- Severe complicating medical illness (e.g. pneumonia)
- Anasarca
- Symptomatic hypotension or syncope
- Refractory to outpatient therapy
- Thromboembolic complications requiring interventions
- Clinically significant dysrhythmias
- Inadequate social support for safe outpatient management
- Persistent hypoxia requiring supplemental oxygen (walk test with SpO_2 monitor can identify patients with occult hypoxia)

YEARS Criteria for Pulmonary Embolism Evaluation
Use in hemodynamically stable patients ≥18 y/o with clinically suspected acute PE, and pregnant patients if DVT excluded. Criteria: clinical signs of deep vein thrombosis (DVT), hemoptysis, and whether PE is the most likely diagnosis. In patients with no YEARS items and D-dimer <1,000 ng/mL, or with 1+ YEARS items and D-dimer <500 ng/mL, PE is excluded. All other patients should have a CT pulmonary angiogram (CTPA)

DEEP VEIN THROMBOSIS

Presentation
- calf pain, unilateral leg swelling/erythema/edema, palpable cord along the deep venous system on exam
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT (may be asymptomatic; bilateral leg presentation unlikely but does not rule out diagnosis; think inferior vena cava (IVC) occlusion if bilateral DVT)
  - further investigation is often needed

Investigations
- use Wells' criteria for DVT to guide investigations (see *Figure 11, ER34*)
- D-dimer is only useful for ruling out DVT, and a D-dimer test result should only be considered in cases where a low-moderate risk patient has a negative test (high sensitivity)
  - high-risk of false positives in: elderly, infection, recent surgery, trauma, hemorrhage, late in pregnancy, liver disease, cancer
- U/S has high sensitivity & specificity for proximal clot but only 73% sensitivity for calf DVT (may need to repeat in 1 wk)
  - if positive – treat for DVT unless anticoagulation is contraindicated
  - if negative and low-risk – rule out DVT
  - if negative and moderate to high-risk – repeat U/S in 5-7 d to rule out DVT

Management
- direct oral anticoagulants (DOAC) can be used in acute management of symptomatic DVT
  - rivaroxaban: 15 mg PO BID for first 21 d; 20 mg PO once daily for remaining treatment (taken with food at the same time each day)
  - apixaban: 10 mg PO BID for first 7 d; 5 mg PO BID for remaining treatment
- low molecular weight heparin (LMWH) unless patient also has renal failure
  - dalteparin 200 IU/kg SC q24 h or enoxaparin 1 mg/kg SC q24 h
  - use of DOAC vs. LMWH for cancer induced VTE; local practice vary
- consider thrombolysis if extensive DVT threatening limb compromise
- IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
- duration of anticoagulation: 3 mo if transient coagulopathy; 6 mo if unprovoked DVT; life-long if ongoing coagulopathy
- calf/distal DVT: local practices vary, no consensus on best treatment; options include a (i) serial venous doppler, start anticoagulation close to proximal system or large clot burden; or (ii) oral anticoagulation, with follow-up in thrombosis clinic

PULMONARY EMBOLISM

Presentation
- dyspnea, pleuritic chest pain, hemoptysis, tachypnea, cyanosis, hypoxia, fever
- clinical signs/symptoms are unreliable for diagnosis and exclusion of PE; investigation often needed

Investigations
- use Wells' criteria for PE to guide investigations (see *Figure 12, ER34*)
- pulmonary embolism rule-out criteria (PERC) score (see EBM on sidebar, Respirology, R21) alone can rule out PE in low-risk patients unless pregnant
- ECG and CXR are useful to rule out other causes (e.g. ACS, pneumonia, pericarditis) or to support diagnosis of PE
  - ECG changes in PE: sinus tachycardia, right ventricular strain (S1Q3T3, see Cardiology and Cardiac Surgery, C10), T wave inversions in anterior and inferior leads (more common sign of RV strain), AFib
  - CXR findings in PE (rarely seen): Hampton's hump (triangular density extending from pleura, sign of pulmonary infarct) or Westermark's sign (dilatation of vessels proximal to an obstruction, with collapse of vessels distal to obstruction, often with a sharp cutoff)
- D-dimer is only useful at ruling out a PE if it is negative in low-moderate risk patients (highly sensitive)
  - if positive D-dimer or high-probability patient, then pursue CT pulmonary angiography or V/Q scan
- CT pulmonary angiography has high sensitivity and specificity for PE, may also indicate an alternative diagnosis
- V/Q scan useful in pregnancy, when CT pulmonary angiography not available, or IV contrast contraindicated

Management
- treatment of PE with anticoagulation and duration of treatment is the same as for DVT (see above)
- thrombolysis indicated in massive PE, which is defined as acute PE with sustained hypotension (sBP <90 mmHg for at least 15 min or requiring inotropic support, not due to a cause other than PE)
- catheter-directed thrombolysis or surgical thrombectomy may be considered in massive PE or if anticoagulation is contraindicated
- often can be treated as an outpatient, may require analgesia for chest pain (narcotic or NSAID)
- admit if hemodynamically unstable, require supplemental O_2, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy, or clinical signs of RV strain on echocardiography
  - referral to medicine for coagulopathy and malignancy workup

Effect of a Diagnostic Strategy Using an Elevated and Age-Adjusted D-Dimer Threshold on Thromboembolic Events in Emergency Department Patients With Suspected Pulmonary Embolism: A Randomized Clinical Trial
JAMA 2021;326:2141-2149.
Purpose: To prospectively validate the safety of a strategy that combines the YEARS rule with the pulmonary embolism rule-out criteria (PERC) rule and an age-adjusted D-dimer threshold.
Methods: Multi-center (n=18), cluster-randomized, crossover, non-inferiority trial in France and Spain. Patients (n=1414) with low clinical risk of PE (<15%) who could not be excluded with PERC or a subjective clinical intermediate risk of PE were included from October 2019 to June 2020, and followed up until October 2020. In intervention period (n=726): PE was excluded without chest imaging in patients with no YEARS criteria and a D-dimer <1000 ng/mL, or in patients with 1+ YEARS criteria and D-dimer level less than age-adjusted threshold. In controls (n=688): PE was excluded without chest imaging if D-dimer level was less than age-adjusted threshold. The primary endpoint was the presence of VTE at 3 mo.
Results: At 3 mo, VTE was diagnosed in 1 patient in the intervention group (0.15% [95% CI, 0.0% to 0.86%]) vs 5 patients in the control group (0.80% [95% CI, 0.26% to 1.86%]). The adjusted difference was -0.64% [1-sided 97.5% CI, -∞ to 0.21%], within the non-inferiority margin).
Conclusions: In ED patients with a suspected PE, the YEARS rule, combined with the age-adjusted D-dimer threshold in PERC-positive patients, did not result in an inferior rate of thromboembolic events, when compared to a conventional diagnostic strategy.

Diagnostic Accuracy of POCUS and CXR in Adults With Symptoms Suggestive of ADHF
JAMA 2019;2:e190703
Purpose: To compare the accuracy of Point-of-Care Lung Ultrasonography (LUS) with the accuracy of CXR in the diagnosis of cardiogenic pulmonary edema.
Methods: Systematic review with inclusion criteria of patients presenting with dyspnea who underwent both LUS and CXR on initial assessment. Imaging results were compared by a clinical expert after either a medical record review or a combination of echocardiography findings and B-type natriuretic peptide (BNP) criteria. Primary outcome was the comparative accuracy of LUS and CXR in diagnosing ADHF as measured by the differences between the 2 modalities in pooled sensitivity and specificity.
Results: 6 studies met the inclusion criteria; a total of 1827 patients. Pooled estimates for LUS were 0.88 for sensitivity and 0.90 for specificity. Pooled estimates for CXR were 0.73 for sensitivity and 0.90 for specificity. The relative sensitivity ratio of LUS, compared with CXR, was 1.2. No difference was found in specificity between tests.
Conclusions: The findings suggest that LUS is more sensitive than CXR in detecting pulmonary edema in ADHF; LUS should be considered as an adjunct imaging modality in the evaluation of patients with dyspnea at risk for ADHF.

Risk Factors for VTE

THROMBOSIS
Trauma, travel
Hypercoagulable, hormone replacement therapy (HRT)
Recreational drugs (IV drug use)
Old (age >60 yr)
Malignancy
Birth control pill
Obesity, obstetrics
Surgery, smoking
Immobilization
Sickness (CHF, MI, nephrotic syndrome, vasculitis)

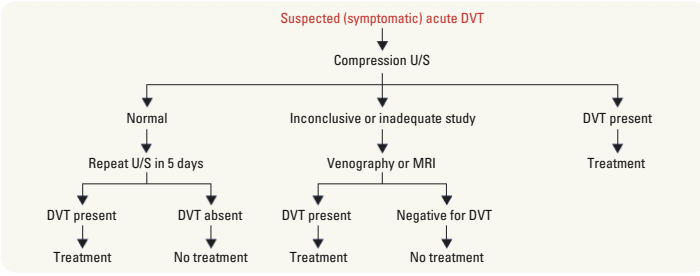


Figure 11. Approach to suspected DVT (with high clinical suspicion and no other cause)

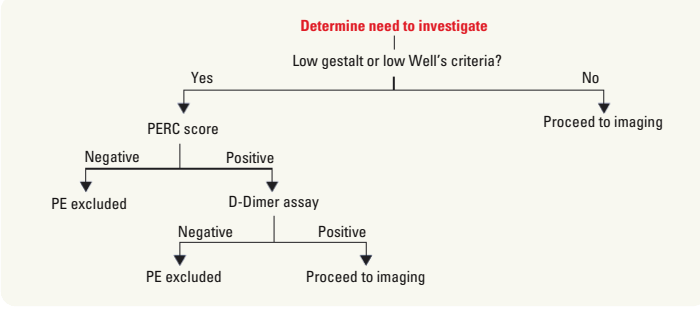


Figure 12. Approach to PE in patients with low clinical suspicion of a PE
Adapted with permission from Dr. Salim R. Rezaie from REBELEM [online]. Original figure can be found at https://rebelem.com/is-it-proper-to-perc-it-up/

Diabetic Emergencies

- see Endocrinology, E13

Diabetic Ketoacidosis

- triad of hyperglycemia, ketosis, and acidosis due to severe insulin deficiency and counter-regulatory hormone excess
- precipitating factors: infection, cardiac or mesenteric ischaemia, MI, intoxication, insulin omission, or SGLT2i (euglycemic DKA)
- clinical features
  - often young, T1DM patients (may rarely be first presentation of undiagnosed T2DM), with symptoms evolving within a day
  - early signs and symptoms: polyuria, polydipsia, malaise, nocturia, weight loss, abdominal pain
  - late signs and symptoms
    - GI: anorexia, nausea, vomiting, increasing abdominal pain
    - neurological: fatigue, drowsiness, stupor, coma
    - respiratory: Kussmaul's respiration, dyspnea (often due to acidosis), fruity ketotic breath
- investigations
  - blood work: CBC, electrolytes, Ca^{2+}, Mg^{2+}, PO_4^{3-}, Cr, BUN, glucose, ketones, osmolality, AST/ALT/ALP, amylase, troponin
  - urine: glucose and ketones
  - ABG or VBG
  - ECG (electrolyte disturbances may predispose to dysrhythmia, MI is rarely a precipitant)
- management
  - rehydration
    - bolus of NS, then high rate NS infusion (beware of overhydration and cerebral edema in pediatric patients (see Pediatrics, P32))
    - beware of a pseudohyponatremia due to hyperglycemia (add 3 Na^+ per 10 glucose over 5.5 mmol/L)
  - potassium
    - essential to avoid hypokalemia: replace KCl 20 mEq/L (only if patient is voiding, adequate renal function, and initial K^+ <5.5 mmol/L)
    - use cardiac monitoring if potassium levels normal or low

Wells' Criteria for DVT

Active cancer	+1
Paralysis, paresis or recent immobilization of leg	+1
Recently bedridden x3 d or major surgery within 4 wk	+1
Local tenderness	+1
Entire leg swollen	+1
Calf swelling 3 cm > asymptomatic leg	+1
Unilateral pitting edema	+1
Collateral superficial veins	+1
Alternative Dx more likely	-2

0: Low probability
1-2: Moderate probability
>3: High probability

Wells' Criteria for PE

Previous Hx of DVT/PE	+1.5
HR >100	+1.5
Recent immobility or surgery	+1.5
Clinical signs of DVT	+3
Alternate Dx less likely than PE	+3
Hemoptysis	+1
Cancer	+1

<2: Low probability
2-6: Intermediate probability
>6: High probability

Signs of PE on CXR
Westermark's sign: abrupt tapering of a vessel on chest film
Hampton's hump: a wedge-shaped infiltrate that abuts the pleura
Effusion, atelectasis, or infiltrates 50% normal
Both signs are specific but not sensitive
A normal CXR in the hypoxic patient warrants a work-up for PE

PERC Score
- Age >50
- HR >100 bpm
- O_2 saturation on room air <95%
- Prior Hx of DVT/PE
- Recent trauma or surgery
- Hemoptysis
- Exogenous estrogen
- Clinical signs suggesting DVT

Score 1 for each question; a score 0/8 means the patient has <1.6% chance of having a PE and avoids further investigation. Caution against using the PERC score in patients with concurrent beta-blocker use, and in pregnant women as the original study excluded both.

D-dimer is only useful if it is negative; negative predictive value >99%

50% of patients with symptomatic proximal DVT will develop PE, often within days to weeks of the event

- insulin
  - critical, as this is the only way to inhibit gluconeogenesis/ketosis
  - do not give insulin if K^+<3.3 mmol/L as insulin will exacerbate hypokalemia
  - continuous infusion at 0.1 U/kg/h
  - once the blood glucose <14 mmol/L, dextrose should be added to the patient's IV fluids
- bicarbonate is not given unless patient is at risk of shock or death (typically pH <7.0)

Hyperosmolar Hyperglycemic State

- hyperosmolar hyperglycemic state (HHS) is characterized by extreme hyperglycemia (33.3 mmol/L) due to relative insulin deficiency, counter-regulatory hormones excess, gluconeogenesis, and dehydration (due to osmotic diuresis)
- clinical features
  - often older, T2DM patients with more comorbid illnesses and larger fluid losses with symptoms evolving over days to weeks, fewer GI symptoms and more neurological deficits than DKA including: mental disturbances, coma, delirium, seizures
  - polyuria, N/V
- investigations
  - blood work: CBC, electrolytes, Ca^{2+}, Mg^{2+}, PO_4^{3-}, Cr, BUN, glucose, ketones, osmolality
  - urine: glucose and ketones
  - VBG
  - find underlying cause: ECG, CXR, blood and urine C&S
  - monitor pH (expected: pH >7.3) and bicarbonate (>18 mEq/L)
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O_2, cardiac monitoring, frequent electrolyte, and glucose monitoring
  - insulin management as per DKA
  - identify and treat precipitating factors, similar to DKA but HHS has also been noted following cardiac surgery and with the use of certain drugs (e.g. diuretics, glucocorticoids, lithium, atypical antipsychotics)
  - admission to medicine

Hypoglycemia

- characterized by Whipple's triad: low plasma glucose, symptoms suggestive of hypoglycemia, prompt resolution of symptoms when glucose administered
- clinical features
  - neuroglycopenic symptoms: headaches, confusion, seizures, loss of consciousness, coma
  - autonomic symptoms: diaphoresis, nausea, tremor, hunger, tachycardia, palpitations
- history and physical exam
  - last meal, known DM, prior similar episodes, drug therapy, and compliance
  - liver/renal/endocrine/neoplastic disease
  - depression, alcohol or drug use
- management
  - check a bedside capillary blood glucose
  - oral sugar if possible (juice, sugar tablets)
  - IV access if oral route not possible
  - D50W 50 mL IV push
    - use lower concentration dextrose solutions in children (rule of 50's: 1 mL/kg of D50W, 2 mL/kg of D25W, 5 mL/kg of D10W, 10 mL/kg of D5W)
  - if IV access and oral replacement not possible, glucagon 1-2 mg IM, repeat in 10-20 min
  - O_2, cardiac, frequent blood glucose monitoring
  - thiamine 300 mg IM (if alcohol use disorder is suspected)
  - full meal as soon as mental status permits
  - if due to long-acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long half-life (may require admission for monitoring)
  - search for cause (common causes include exogenous insulin, alcohol, or sulfonylureas)

Oral Direct Thrombin Inhibitors or Oral Factor Xa Inhibitors for the Treatment of Pulmonary Embolism
Cochrane DB Syst Rev 2023:CD010957
Purpose: Assess effectiveness of oral direct thrombin inhibitors and oral factor Xa inhibitors for long-term treatment of PE as compared to conventional anticoagulants.
Methods: Systematic review of RCTs in patients with confirmed PE receiving oral direct thrombin inhibitors or factor Xa inhibitors for minimum 3 mo.
Results: Ten RCTs (n=13,073). No difference in the effectiveness of oral factor Xa inhibitors vs. standard anticoagulation in preventing recurrent PE (OR 0.95; 95% CI, 0.66-1.03), recurrent VTE (OR 0.83; 95% CI, 0.66-1.25), DVT (OR 0.77; 95% CI, 0.48-1.25), all-cause mortality (OR 1.16; 95% CI, 0.79-1.70), or major bleeding (OR 0.71; 95% CI, 0.36-1.41).
Conclusions: Moderate-low evidence suggests there is little to no difference between DOACs compared to conventional anticoagulation in the treatment of PE.

Criteria for DKA Dx
Hyperglycemia
Metabolic acidosis
Hyperketonemia or Ketonuria

Signs and Symptoms of DKA

Diuresis, dehydration, drowsy, delirium, dizziness
Kussmaul's breathing, ketotic breath
Abdominal pain, anorexia

Precipitating Factors in DKA

The 5 Is
Infection
Ischaemia
Infarction
Intoxication
Insulin missed

Causes of Hypoglycemia
Most common: excessive insulin use in setting of poor PO intake
Common: alcohol intoxication, sepsis, liver disease, oral anti-hyperglycemics
Rare: insulinomas, hypopituitarism, adrenal insufficiency, medication side effects

Cerebral edema may occur if hyperosmolality is treated too aggressively

Electrolyte Disturbances

- see Nephrology, NP8

Table 20. Electrolyte Disturbances

Electrolyte Disturbance	Common Causes	Symptoms	Treatment	Special Considerations
Hypernatremia	Inadequate H_2O intake (elderly/disabled) or inappropriate excretion of H_2O (diuretics, Li, and diabetes insipidus)	Lethargy, weakness, irritability, and edema; seizures and coma occur with severe elevations of Na^+ levels (>158 mmol/L)	Salt restrict and give normal saline until hemodynamically stable. Use half-normal saline once vitals are stable	No more than 12 mmol/L in 24 h drop in Na^+ (0.5 mmol/L/h) due to risk of cerebral edema, seizures, death
Hyponatremia	Hypovolemic (GI, renal, skin, blood fluid loss), euvolemic (syndrome of inappropriate antidiuretic hormone secretion (SIADH)/ stress, adrenal insufficiency, hypothyroid, diet/intake), hypervolemic (CHF, cirrhosis, nephrotic syndrome)	Neurologic symptoms secondary to cerebral edema, headache, seizure, decreased LOC, depressed reflexes; chronic milder than acute	Hypovolemic: normal saline Euvolemic: restrict water, eliminate underlying cause Hypervolemic: restrict fluid and sodium, loop diuretic if severe 3% hypertonic saline if seizure or coma	Limit total rise to 8 mmol/L in 24 h (0.25 mmol/L/h maximum) as patients are at risk of osmotic demyelinating syndrome (ODS)
Hyperkalemia	Rhabdomyolysis, insulin deficiency, metabolic acidosis (e.g. acute renal failure, missed dialysis), medications (e.g. K^+ sparing diuretics, ACEI, NSAIDs)	Nausea, palpitations, dysrhythmias, muscle stiffness, areflexia	Protect heart: calcium gluconate Shift K^+ into cells: D50W + insulin, $NaHCO_3$, salbutamol Remove K^+: fluids + furosemide, dialysis	High-risk of dysrhythmia - ECG: peaked/ narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, sine wave, AV block, VFib, bradycardia
Hypokalemia	Metabolic alkalosis (e.g. diarrhea), insulin, diuretics (except K^+ sparing), anorexia, salbutamol	N/V, fatigue, muscle cramps, constipation, dysrhythmias	K-Dur®, K^+ sparing diuretics, IV solutions with 20-40 mEq/L KCl over 3-4 h	ECG: U waves most important, flattened/ inverted T waves, prolonged QT, depressed ST May need to restore Mg^{2+}
Hypercalcemia	Hyperparathyroidism and malignancy account for ~90% of cases, medications (e.g. thiazide diuretics, lithium)	Multisystem including CVS, GI (groans), renal (stones), rheumatological, MSK (bones), psychiatric (moans)	Isotonic saline (+ furosemide if hypervolemic) Bisphosphonates, dialysis, chelation (Ethylenediaminetetraacetic acid (EDTA) or oral PO_4^{3-})	Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy
Hypocalcemia	Iatrogenic, hypoalbuminemia, liver dysfunction, primary hypo-parathyroid hormone, recent thyroid surgery	Laryngospasm, hyperreflexia, paresthesia, tetany, Chvostek's and Trousseau's sign	Acute (ionized Ca^{2+}<0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion	Prolonged QT interval can arise (leading to dysrhythmia as can upper airway obstruction)

Hypertensive Emergencies

Hypertensive Emergency (Hypertensive Crisis)

- definition: severe elevation of BP with evidence of end-organ damage (CNS, retinal, CVS, renal, GI)
- etiology
  - essential HTN, emotional exertion, pain, use of sympathomimetic drugs (cocaine, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), pheochromocytoma, pregnancy
- clinical features

Table 21. Signs and Symptoms of Hypertensive Emergencies

	CNS	Retinal	Renal	Cardiovascular	Gastrointestinal
Complication	Stroke/TIA, headache, altered mental status, seizures, hemorrhage	Vision change, hemorrhage, exudates, papilledema	Nocturia, elevated Cr, proteinuria, hematuria, oliguria	Ischaemia/angina, infarction, dissection (back pain), CHF	N/V, abdominal pain, elevated liver enzymes

- investigations
  - blood work: CBC, electrolytes, BUN, Cr
  - urinalysis
  - peripheral blood smear: to detect microangiopathic hemolytic anemia
  - CXR: if SOB or chest pain
  - ECG, troponins, creatine kinase (CK): if chest pain
  - CT head: if neurological findings or severe headache
    - toxicology screen if sympathomimetic overdose suspected (not needed if patient admits to taking it)
- management
  - in general, strategy is to gradually and progressively reduce BP in 24-48 h
  - lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually labetalol)
  - if preeclampsia, immediately consult obstetrician-gynecologist (OB/GYN) (see Obstetrics, OB26) and give magnesium
  - establish arterial line; transfer to ICU for further reduction in BP under monitored setting
  - in case of ischaemic stroke: do not rapidly reduce BP, maintain BP >150/100 for 5 d
  - in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
  - in case of excessive catecholamines: avoid β-blockers (except labetalol)
  - in case of ACS: address ischaemia initially, then BP

HELLP Syndrome (seen only in preeclampsia/eclampsia)

Hemolytic anemia
Elevated **L**iver enzymes
Low **P**latelet count

Catecholamine-Induced Hypertensive Emergencies
Avoid use of non-selective β-blockers as they inhibit β-mediated vasodilation and leave α-adrenergic vasoconstriction unopposed

Hypertensive Urgency (Severe Asymptomatic Hypertension)

- elevated BP (sBP > 180, dPB > 120), but no evidence of end organ injury
- most will have a mild headache, non-specific vision changes, and/or nausea
- search carefully for end organ injury; measure BP properly (measure in a quiet room and bilaterally)
- modify or initiate anti-hypertensives and follow up with primary care team
- no proven benefit from rapid reduction of blood pressure (rapid reduction can lead to MI, AKI, and/or CVA)

Table 22. Commonly Used Agents for the Treatment of Hypertensive Crisis

Drug	Dosage	Onset of Action	Duration of Action	Adverse Effects*	Special Indications
VASODILATORS					
Sodium Nitroprusside (vascular smooth muscle dilator)	0.25-10 µg/kg/min	Immediate	3-5 min	N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome	Use in combination with β-blockers (e.g. esmolol) in aortic dissection Caution with high ICP and azotemia
Nicardipine (calcium channel blocker)	5 mg/h IV, then increase by 2.5 mg/h q5-10 min (max 15 mg/h)	15-30 min	40 min	Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, renal failure, eclampsia, sympathetic crisis)	Most hypertensive emergencies (note: IV form not available in Canada; oral form does not have a reliable response for acute settings) Caution with acute CHF
Nitroglycerin	5-20 µg/min IV	1-2 min	3-5 min	Hypotension, bradycardia, headache, lightheadedness, dizziness	MI, pulmonary edema
Hydralazine	5-10 mg IV/IM q20 min (max 20 mg)	5-20 min	2-6 h	Dizziness, drowsiness, headache, tachycardia, Na^+ retention	Eclampsia
ADRENERGIC INHIBITORS					
Labetalol	20 mg IV bolus q10 min or 0.5-2 mg/min	5-10 min	3-6 h	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Usually first choice Most hypertensive emergencies (especially eclampsia) Avoid in acute CHF, heart block >1st degree
Esmolol	250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat	1-2 min	10-20 min	Hypotension, nausea, bronchospasm	Aortic dissection, acute MI supraventricular tachycardia (SVT) dysrhythmias, perioperative HTN Avoid in acute CHF, heart block >1st degree
Phentolamine	5-15 mg q5-15 min	1-2 min	3-10 min	Tachycardia, headache, flushing	Catecholamine excess (e.g. pheochromocytoma, unopposed α - e.g. cocaine)

*Hypotension may occur when using any of these agents

With CNS manifestations of severe HTN, it is often difficult to differentiate causal relationships (i.e. HTN could be secondary to a cerebral event with an associated Cushing reflex)

Acute Coronary Syndrome

- see Cardiology and Cardiac Surgery, C36
- definition: new onset of chest pain, or acute worsening of previous chest pain, or chest pain at rest with:
  - negative cardiac biomarkers and no ECG changes = unstable angina (UA)
  - positive cardiac biomarkers (elevated troponin), NSTEMI on ECG, ± other changes (NSTEMI)
  - positive cardiac biomarkers (elevated troponin) and STEMI on ECG
- occlusion myocardial infarction: new paradigm, supports ECG findings suggesting acute coronary artery occlusion without a ST elevation on ECG; examples include Wellens Syndrome, De Winter T waves and hyperacute T waves
- investigations
  - ECG STAT (as soon as history suggests possible ACS), serial troponins (2-6 h after symptom onset), CXR (to rule out other causes of the patient's presentation)
  - serial ECGs improve sensitivity; consider in patients who have pain highlight suggestive of ACS
- management
  - stabilize: ABCs, oxygen, IV access, cardiac monitors, oximetry
  - ASA 162-325 mg chewed and swallowed
  - nitroglycerin 0.3 mg SL q5 min x 3; IV only if persistent pain, CHF, or hypertensive
    - contraindications: hypotension, phosphodiesterase inhibitor use, right ventricular infarctions (1/3 of all inferior MIs, as these MIs are preload-dependent)
    - symptom relief only, no mortality benefit
  - anticoagulation: choice of anticoagulation (unfractionated heparin, LMWH, or fondaparinux) and additional antiplatelet therapy (clopidogrel, ticagrelor, or prasugrel) depends on STEMI vs. NSTEMI and reperfusion strategy
  - early cardiology consult for reperfusion therapy
    - UA/NSTEMI: early coronary angiography recommended if high thrombolysis in MI (TIMI) risk score
    - STEMI: primary percutaneous coronary intervention (PCI) (within 90 min) preferred; thrombolytics if PCI unavailable within 120 min of medical contact, symptoms <12 h and no contraindications

Sepsis

- see Infectious Diseases, ID20 and Respirology, R32
- definitions
  - overall, sepsis can be thought of as a life-threatening organ dysfunction caused by a dysregulated host response to infection; however, definitions exist on a spectrum, as outlined below
  - systemic inflammatory response syndrome (SIRS): two or more of T >38°C or <36°C, HR >90, RR >20, WBC >12
  - sepsis: SIRS and suspected or present source of infection
  - septic shock: sepsis and either initial lactate >4 or hypotension
  - qSOFA score ≥2: high risk for in-hospital mortality (see Infectious Diseases, ID20)
  - although the presence of a positive qSOFA should alert clinicians to the possibility of sepsis in all resource settings, it should not be used as a single screening tool given its poor sensitivity.
- management
  - early recognition of sepsis and investigations to locate source of infection
  - identify severe sepsis with lactate or evidence of tissue hypoperfusion (evaluate tissue perfusion at bedside with cap refill, mental status, or urine output)
  - sepsis standard operating procedures, initially specified as Early Goal Directed Therapy have evolved to "usual care" which includes a standard approach with components of the sepsis bundle, early identification, lactate, cultures, antibiotics, and fluids
  - treatment priorities:
    - ABCs, monitors, lines
    - aggressive fluid resuscitation; consider ventilatory and early inotropic support
    - cultures, then early empiric appropriate antibiotics - consider broad spectrum and atypical coverage
    - source control (e.g. remove infected Foley or surgery for ischaemic gut)
    - monitor adequate resuscitation with vital signs, inferior vena cava on U/S (if patient is mechanically ventilated), urine output, and serial measurement of serum lactate
    - in patients presenting with septic shock, goal-directed therapy and aggressive management should not be delayed while waiting for lab values
    - patients failing initial therapy should be resuscitated more aggressively (e.g. use of vasopressors, inotropic therapy, blood transfusion)
      - consider glucocorticoids if treatment refractory hypotension for relative adrenal insufficiency
      - look for other causes of shock if not responding to treatment (use protocols, such as PoCUS RUSH, to assess for free fluid, ectopic pregnancy, pneumothorax, AAA, tamponade)

Surviving Sepsis Campaign 1 Hour Bundle
J Intensive Care Med 2018;44:925-928
Update sepsis bundle from 3 h to 1 h time frame with time zero being time of triage in the ED
Actions include:
- Measure lactate level. Remeasure if initial lactate is >2 mmol/L
- Obtain blood cultures prior to administration of antibiotics
- Administer broad spectrum antibiotics
- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate >4 mmol/L
- Apply vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain MAP >65 mmHg

Stroke and Transient Ischaemic Attack

- see Neurology, N51
- definitions
  - stroke: sudden loss of brain function due to ischaemia (87%) or hemorrhage (13%) with persistence of symptoms >24 h or neuroimaging evidence
  - TIA: transient episode of neurologic dysfunction from focal ischaemia without acute infarction or neuroimaging evidence
- clinical features

Table 23. Signs and Symptoms of Stroke

	General	Language/ Throat	Vision	Coordination	Motor	Sensation	Reflex
Signs/ Symptoms	Decreased LOC (rare), changed mental status, confusion, neglect	Dysarthria, aphasia, swallowing difficulty	Diplopia, eye deviation, asymmetric pupils, visual field defect	Ataxia, intention tremor, lack of coordination	Increased tone, loss of power, spasticity	Loss of sensation	Hyper-reflexia, clonus

- patients with hemorrhagic stroke resulting in subarachnoid hemorrhage can present with sudden onset thunderclap headache that is usually described as "worst headache of life" and can often recall the exact moment their headache started
- stroke mimickers: seizure, Todd's paresis (period of partial or complete paralysis following a seizure), migraine, hypoglycemia, peripheral nerve injury, Bell's palsy, tumour, syncope, somatic symptom disorder

Table 24. Stroke Syndromes

Region of Stroke	Stroke Syndrome
Anterior Cerebral Artery	Contralateral hemianesthesia and hemiparesis (legs > arms/face), gait apraxia, altered mental status, impaired judgement
Middle Cerebral Artery	Contralateral hemianesthesia and hemiparesis (arms/face > legs), contralateral homonymous hemianopsia, ipsilateral gaze
Posterior Cerebral Artery	Contralateral homonymous hemianopsia, cortical blindness, impaired memory
Vertebrobasilar Artery	Wide variety of cranial nerve, cerebellar, and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypoesthesia, syncope, ataxia Loss of pain and temperature sensation in ipsilateral face and contralateral body

Seven Causes of Emboli from the Heart
- AFib
- MI
- Endocarditis
- Valvular disease
- Dilated cardiomyopathy
- Left heart myxoma
- Prosthetic valves

Differentiation of Upper Motor Neuron (UMN) Disease vs. Lower Motor Neuron (LMN) Disease

Category	UMN Disease	LMN Disease
Muscular deficit	Muscle groups	Individual muscles
Reflexes	Increased	Decreased/ absent
Tone	Increased	Decreased
Fasciculations	Absent	Present
Atrophy	Absent/ minimal	Present
Plantar Response	Upgoing	Downgoing

Investigations
- CBC, electrolytes, blood glucose, coagulation studies ± cardiac biomarkers ± toxicology screen
- CT angiography and perfusion of the head and neck
- ECG: rule out AFib, acute MI as source of emboli
- other imaging: if you are suspicious of a TIA a plain CT followed by carotid Doppler, outpatient CT angiography neck and/or head, magnetic resonance angiography (MRA) can be arranged based on local resources

Management
- ABCs; intubation with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protective reflexes
- for ischaemic CVA thrombolysis (rt-PA, e.g. alteplase): immediate assessment for eligibility; need acute onset, <4.5 h from last seen normal AND compatible physical findings AND no evidence of hemorrhage on CT scan
  - thrombectomy: may be an option in some centres as an alternative to thrombolysis in the first 4.5 to 6 h, and in some instances up to 24 h after symptom onset or last seen normal
- dual antiplatelet therapy for 21 d
  - this should be initiated for high risk TIA in the ED
- elevating head of bed if suspicious of increased ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV ± cardiac monitoring
  - judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischaemic penumbra)
- BP control: only treat severe HTN (sBP >200 mmHg, dBP >120 mmHg, MAP >140 mmHg) or HTN associated with hemorrhagic stroke transformation, cardiac ischaemia, aortic dissection, or renal damage; use IV nitroprusside or labetalol
- glycemic control serum glucose of 7.8-10 mmol/L
- cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- consult neurosurgery, neurology, medicine as indicated
- following acute ischaemic event:
  - antiplatelet agents to: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin® (1st line); clopidogrel, Aggrenox® (2nd line)
  - consider anticoagulation: if Afib present or if immobile for DVT prophylaxis
  - follow-up for consideration of carotid endarterectomy, cardiovascular risk optimization

If a patient presents within 4.5 h of onset of disabling neurological deficits >60 min with no signs of resolution, they may be a candidate for thrombolysis. Do brief assessment and order CT head STAT

Use the NIH Stroke Scale/Score (NIHSS) to assess stroke severity in an acute setting and predict clinical outcomes.

Absolute Exclusion Criteria for Tissue Plasminogen Activator (tPA)
- Suspected subarachnoid hemorrhage
- Previous intracranial hemorrhage
- Cerebral infarct or severe HI within the past 3 mo
- sBP >185 mmHg, or dBP >110 mmHg
- Bleeding diathesis
- Prolonged PT >15 s or INR >1.7
- Platelet count <100000
- Heparin received within last 48 h
- Current use of thrombin inhibitors or direct factor Xa inhibitors
- Blood glucose <2.8 mmol/L (<50 mg/dL)
- Intracranial hemorrhage on CT or large volume infarct

Relative Exclusion Criteria for tPA
- Only minor or rapidly improving symptoms
- Pregnancy
- GI or urinary hemorrhage within the past 21 d
- Seizure at onset causing postictal impairments

Otolaryngological Presentations and Emergencies

- ear symptoms: otalgia, aural fullness, otorrhea, hearing loss, tinnitus, vertigo, pruritus, fever
- risk factors for hearing loss: Q-tip use, hearing aids, headphones, occupational noise exposure

Dizziness and Vertigo
- distinguish four types of dizziness: vertigo ("room spinning"), lightheadedness ("disconnected from environment"), presyncope ("almost blacking out"), dysequilibrium ("unstable," "off-balance")
- broad differential and diverse management (see Family Medicine, FM28 and Otolaryngology, OT6)
- rule out stroke
- consider adverse drug events

Otalgia (see Otolaryngology, OT6)
- differential diagnosis
  - infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis externa in patients with diabetes, herpes simplex/zoster, auricular cellulitis, external canal abscess, dental disease, referred pain from neck and/or jaw
  - others: trauma, temporomandibular joint dysfunction, neoplasm, foreign body, cerumen impactions, trigeminal neuralgia, granulomatosis with polyangiitis
- inspect for otorrhea, palpate outer ear/mastoid, otoscopic examination to look for bulging erythematous tympanic membrane, perforation, membrane retraction, infiltration, vesicles, ulcers, masses, lesions
- C&S of ear canal discharge, if present
- CT head if suspicion of mastoiditis, malignant otitis externa
- antibiotics/antifungals/antivirals for respective infections

Hearing Loss (see Otolaryngology, OT7)
- differentiate conductive vs. sensorineural hearing loss
- rule out sudden sensorineural hearing loss (SSNHL), a medical emergency requiring high dose steroids and urgent referral
- an elderly patient presenting with unilateral tinnitus or SSNHL must be presumed to have an acoustic neuroma (vestibular schwannoma) until proven otherwise
- consider audiogram and referral to or follow-up with family physician

Epistaxis

- see Otolaryngology, OT27
- 90% of nosebleeds stem from the anterior nasal septum (Kiesselbach's plexus located in Little's area)
- can be life-threatening

Etiology
- most cases of epistaxis are caused by trauma (e.g. digital, blunt, foreign bodies)
- other causes: barometric changes, nasal dryness, chemicals (e.g. cocaine, Otrivin®), or systemic disease (e.g. coagulopathies, HTN)

Investigations
- blood work: CBC, PT/PTT/INR/platelet function assay (if suspicious of bleeding disorder) as needed
- imaging: x-ray, CT as needed (e.g. trauma)

Treatment
- goals of treatment: localize bleeding and achieve haemostasis
- first-aid: ABCs, clear clots by blowing nose or suctioning, lean forward, pinch cartilaginous portion of nose for 20 min twice (note: best to use a compression device and not the patient's fingers)
- assess blood loss: vitals; if severe bleeding or unstable patient IV NS, cross match 2 units pRBC
- if first aid measures fail twice, proceed to packing
- apply an anterior pack
  - clear nose of any clots
  - apply topical anesthesia/vasoconstrictors (lidocaine with epinephrine, cocaine, or soaked pledgets)
  - insert either a traditional Vaseline® gauze pack or a commercial nasal tampon or balloon
  - N.B. if the site of bleeding is identified, cautery with silver nitrate can be performed as an alternative to packing (only cauterize one side of the septum because if both are cauterized this can lead to septal perforation)
  - if bleeding stops, arrange follow-up in 48-72 h for reassessment and pack removal
  - if packing both nares, prophylactic anti-staphylococcal antibiotics to prevent sinusitis or TSS
- if suspect posterior bleed or anterior packing does not provide haemostasis, consult ENT for posterior packing and further evaluation
  - though posterior packing may be placed by an ED physician, it requires monitoring; can cause significant vagal response and posterior bleeding source can lead to significant blood loss, therefore usually requires admission

Disposition
- discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. topical vaseline, humidifiers, saline spray, avoiding irritants, managing HTN)
- admission: severe cases of refractory bleeding, and most cases of posterior packing

Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

Complications of Nasal Packing
- Hypoxemia
- TSS
- Aspiration
- Pharyngeal fibrosis/stenosis
- Alar/septal necrosis

Tranexamic Acid For Patients with Nasal Haemorrhage (Epistaxis)
Cochrane DB Syst Rev 2018: CD004328
Purpose: Determine the effects of tranexamic acid compared to placebo, no additional intervention or any other haemostatic agent in the management of patients with epistaxis.
Methods: Systematic review of RCTs comparing tranexamic acid, in addition to standard care, compared to usual care plus placebo in adults and children.
Results: 6 RCTs, 692 participants. Oral (RR 0.73, 95% CI 0.55-0.96) and topical (RR 0.66, 95% CI 0.41-1.05) reduced risk of re-bleeding compared to placebo. There was no difference in time to stop initial bleeding. The proportion of patients whose bleeding stopped within 10 min was higher with topical tranexamic acid than other haemostatic agents (RR 2.35, 95% CI 1.90-2.92).
Conclusions: Moderate-quality evidence that risk of re-bleeding with oral or topical tranexamic acid, in addition to usual care, is lower in adult patients with epistaxis, compared to placebo with usual care. Further, topical tranexamic acid is probably better than other topical agents in stopping bleeding in the first 10 min.

Gynecologic/Urologic Emergencies

Vaginal Bleeding

- see Gynecology, GY20 and Obstetrics, OB14

Etiology
- pregnant patient (note: unless proven otherwise, all female patients of possible childbearing age should be assumed to be pregnant and to have an ectopic pregnancy)
  - 1st/2nd trimester: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause), subchorionic hemorrhage
  - 2nd/3rd trimester: placenta previa, placental abruption, premature rupture of membranes, preterm labour
  - other: trauma, bleeding cervical polyp, passing of mucous plug, incompetent cervix, cervicitis, endometritis
- postpartum
  - causes of postpartum hemorrhage (Four T's): tone (uterine atony), tissue (retained placenta), trauma (laceration, uterine inversion), and thrombin (coagulopathy)
- non-pregnant patients
  - structural (PALM- polyps, adenomyosis, leiomyoma, malignancies/hyperplasia)
  - non-structural (COEIN - coagulopathy, ovulatory, endometrial, iatrogenic, not yet diagnosed)

History
- characterize bleeding (frequency, duration, number of pads/tampons, types of pads used, cyclicity)
- pain, if present (OPQRSTUV)
- menstrual history, sexual history, STI history, syncope/presyncope, malignancy history, family history, hematological history, cardiac history, abdominal history, history of previous ectopic pregnancy, smoking history, IUD or OCP use
- details of pregnancy, including gush of fluid and fetal movement (>20 wk)

Physical Exam
- ABCs (especially noting postural BP/HR)
- abdominal examination (signs of peritoneal pathology, tenderness, distension, mass)
- speculum examination (NOT if 2nd/3rd trimester bleeding as may worsen bleeding; perform only if placenta previa has been ruled out with U/S)
  - look for active bleeding, trauma/anomaly, and cervical dilatation
  - in 1st trimester, removing a clot at cervical os can help slow bleeding
  - a dilated os is highly suggestive of incomplete abortion
- bimanual examination (NOT if 2nd/3rd trimester bleeding as may worsen bleeding; perform only if placenta previa has been ruled out with U/S)
  - cervical motion tenderness, size of uterus, cervical length/dilatation
- sterile gloves and speculum if pregnant and beyond the first trimester
- POCUS: rule in intra-uterine pregnancy, check for free fluid in pelvis/right upper quadrant (RUQ)/left upper quadrant (LUQ), consider assessment of fluid responsiveness (intra-hepatic IVC collapsibility, carotid flow measurement)

Investigations
- β-hCG test for all patients with childbearing potential
- CBC, blood and Rh type, quantitative β-hCG, PTT, INR
- type & cross if significant blood loss
- transvaginal U/S (rule out ectopic pregnancy and spontaneous abortion)
- abdominal U/S (rule out placenta previa, fetal demise, or retained products postpartum)

Management
- ABCs
- cardiac monitors if unstable
- Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
- 1st/2nd trimester pregnancy
  - ectopic pregnancy: definitive treatment with surgery or methotrexate
  - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
  - U/S indeterminate or β-hCG >1000-2000 IU: further workup and/or gynecology consult
  - abortions: if complete, discharge if stable; for all others, consult gynecology
- 2nd/3rd trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type & cross 4 units of blood, consult OB/GYN immediately
  - uterine atony: oxytocin 10 units IM or 40 units in 1L wide open until the uterus is firm, then 200 cc/hr
  - genital tract trauma: visual inspection and repair
  - retained products of conception: bimanual or speculum
  - coagulopathy: TXA may be helpful
  - tamponade: use Bakri tube or foley catheter to tamponade, if other measures not successful
- non-pregnant
  - if unstable admit to gynecology for IV hormonal therapy, possible dilation and curettage
  - non-structural abnormalities
    - tranexamic acid to stabilize clots
    - medroxyprogesterone acetate 10 mg PO once daily x10 d, warn patient of a withdrawal bleed
  - stable structural abnormalities (fibroids, polyps, endometrial thickening, adenomyosis), outpatient gynecology referral once stable

Disposition
- decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult OB/GYN for patients requiring admission
- if patient can be safely discharged, ensure follow-up with family physician or OB/GYN
- instruct patient to return to ED for increased bleeding or presyncope

Vaginal bleeding can be life-threatening. Always start with ABCs and ensure your patient is stable

An ectopic pregnancy can be ruled out by confirming an intrauterine pregnancy by bedside U/S unless the patient is using *in vitro* fertilization (IVF) due to the associated high-risk of heterotopic pregnancy

Vaginal bleeding (and its underlying causes) can be a very distressing event for patients; ensure appropriate support is provided

Pregnant Patient in the ED

Table 25. Complications of Pregnancy

Trimester	Fetal	Maternal
First 1-12 wk	Pregnancy failure Spontaneous abortion Fetal demise Gestational trophoblastic disease	Ectopic pregnancy Anemia Hyperemesis gravidarum UTI/pyelonephritis
Second 13-27 wk	Disorders of fetal growth Intrauterine growth restriction Oligo/polyhydramnios	Gestational DM Rh incompatibility UTI/pyelonephritis Cervical incompetence
Third 28-41 wk	Vasa previa	Preterm labour/preterm premature rupture of the membranes Preeclampsia (hypertension in pregnancy)/eclampsia Placenta previa Placental abruption Uterine rupture DVT/PE

Nephrolithiasis (Renal Colic)

• see Urology, U19

Epidemiology and Risk Factors
- 10% of population (twice as common in males)
- recurrence 50% at 5 yr
- peak incidence 30-50 yr
- 75% of stones <4 mm pass spontaneously within 2 wk, larger stones may require consultation

Kidney Stones
80% calcium oxalate
10% struvite
10% uric acid

Clinical Features
- urinary obstruction → upstream distention of ureter or collecting system → severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- writhing, N/V, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis
- peritoneal findings/anterior abdominal tenderness usually absent (if present, consider renal pelvis rupture or other cause)

Obstruction + Infection
= Urological Emergency
Urgent urology consult + IV fluids + broad spectrum antibiotics

Differential Diagnosis of Renal Colic
- acute ureteric obstruction
- acute abdomen: biliary, bowel, pancreas, AAA, diverticulitis
- urogynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, testicular torsion
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1): herpes zoster, nerve root compression

Investigations
- CBC: elevated WBC in presence of fever may support an infectious cause
- electrolytes, Cr, BUN to assess renal function
- U/A: routine and microscopy (WBCs, RBCs, crystals), C&S
- non-contrast CT is the study of choice (better specificity and sensitivity)
- consider abdominal U/S in females of childbearing age, children, or if patient has another contraindication to CT scanning: may demonstrate stone(s), hydronephrosis, debris in the collecting system, reduced cortical vascularity, abnormal renal parenchyma
- AXR will identify large radiopaque stones (calcium, struvite, and cystine stones) but may miss smaller stones, uric acid stones, or stones overlying bony structures; consider as an initial investigation in patients who have a history of radiopaque stones and similar episodes of acute flank pain, carry out with U/S (CT necessary if film is negative).

Indications for Admission to Hospital
- Intractable pain
- Fever (suggests infection) or other evidence of pyelonephritis
- Single kidney with ureteral obstruction
- Bilateral obstructing stones
- Intractable vomiting
- Compromised renal function

Management
- analgesics: NSAIDs (usually ketorolac (Toradol®), preferable over opioids), antiemetics, IV fluids if indicated
- urology consult indicated, especially if stone >5 mm, or if patient has signs of obstruction leading to renal dysfunction or infection
- α-blocker (e.g. tamsulosin) may be helpful to increase stone passage in select cases

Disposition
- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and able to tolerate oral medications
- may advise hydration and limitation of protein, sodium, oxalate, and alcohol intake

Ophthalmologic Emergencies

• see Ophthalmology, OP5

History and Physical Exam
- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital x-rays, U/S, or CT scan to exclude presence of intraocular metallic foreign body
- ask about sexual partners and exposure of eye(s) to bodily fluids (semen, urine, blood, vaginal fluids, saliva, etc.)
- visual acuity in both eyes, pupils, extraocular structures, extraocular movements, fundoscopy, tonometry, slit lamp exam, visual fields

Contraindications to Pupil Dilation
- Shallow anterior chamber
- Iris-supported lens implant
- Potential neurological abnormality requiring pupillary evaluation
- Caution with CV disease – mydriatics can cause tachycardia

Management of Ophthalmologic Foreign Body
- for a chemical injury: copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab, sterile needle, or electric burr tool
- antibiotic drops if indicated (e.g. organic foreign body)
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only

- tetanus prophylaxis
- ophthalmology should see in follow-up or ED consult if globe penetration suspected

Table 26. Differential Diagnosis of Red Eye in the Emergency Department

Symptom	Possible Serious Etiology
Light Sensitivity	Iritis, keratitis, abrasion, ulcer
Unilateral	Above + herpes simplex, acute angle closure glaucoma
Significant Pain	Above + scleritis
White Spot on Cornea	Corneal ulcer
Non-Reactive Pupil	Acute glaucoma, iritis
Copious Discharge	Gonococcal conjunctivitis
Blurred Vision	All of the above

Table 27. Select Ophthalmologic Emergencies

Condition	Signs and Symptoms	Management
Acute Angle Closure Glaucoma	Unilateral red, painful eye Decreased visual acuity, halos around lights Fixed, mid-dilated pupil N/V Marked increase in intraocular pressure (IOP) (>40 mmHg) Shallow anterior chamber ± cells	Ophthalmology consult for laser iridotomy Medications: AABCDE/EAT PAL α-agonist: epinephrine α2-agonist: apraclonidine β-blocker: timolol Cholinomimetic: pilocarpine Diuretic: acetazolamide, mannitol Eicosanoid: latanoprost
Corneal Abrasion	Pain, redness, tearing, photophobia, foreign body sensation De-epithelialized area stains with fluorescein dye	Most clear spontaneously within 24-48 h If due to foreign body, remove under magnification using local anesthetic and sterile needle, or consult ophthalmology for removal under magnification Topical antibiotic (drops or ointment)
Chemical Burn	Known exposure to acids or alkali (worse) Pain, decreased visual acuity Vascularization or defects of cornea Iris and lens damage	Irrigate site of accident with NS with eyelid retracted until neutral pH achieved Sweep fornices Cycloplegic drops and topical antibiotics
Orbital Cellulitis	Red, painful eye, decreased visual acuity Headache, fever Lid erythema, edema, and difficulty opening eye Conjunctival injection and chemosis Proptosis, opthalmoplegia ± RAPD	Admission, ophthalmology consult Blood cultures, orbital CT IV antibiotics (ceftriaxone + vancomycin) Drainage of abscess
Retinal Artery Occlusion	Sudden, painless, monocular vision loss RAPD Cherry red spot and retinal pallor on fundoscopy if central retinal artery occlusion	Restore blood flow <2 h Massage globe Decrease IOP (topical β-blockers, inhaled O_2/CO_2 mix, IV Diamox®, IV mannitol, drain aqueous fluid)
Retinal Vein Occlusion	Painless, monocular, gradual, or sudden vision loss ±RAPD On fundoscopy: "blood and thunder" appearance, diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema	Ophthalmology consult for retinal laser photocoagulation, anti-VEGF, and/or corticosteroid injection
Retinal Detachment	Flashes of light, floaters, and curtains of blackness/peripheral vision loss Painless Loss of red reflex, decreased IOP Detached areas are grey Visible detachment orbital POCUS ± RAPD	Ophthalmology consult for scleral buckle/pneumatic retinopexy

Other Ophthalmologic Emergencies
Infectious: Red eye, endophthalmitis, hypopyon
Trauma: Globe rupture, orbital blow-out fractures, corneal injuries, eyelid laceration, hyphema, lens dislocation, retrobulbar hemorrhage
Painful vision loss: Acute iritis, corneal abrasion, globe rupture, lens dislocation, retrobulbar hemorrhage, optic neuritis, temporal arteritis, endophthalmitis, keratitis
Painless vision loss: Central retinal vein occlusion, amaurosis fugax, occipital stroke

POCUS for the Diagnosis of Retinal Detachment: A Systematic Review and Meta-Analysis
Acad Emerg Med 2019;26:931-939
Purpose: POCUS has been suggested to identify retinal detachment rapidly. The primary outcome for this review was to determine the test characteristics of POCUS for the diagnosis of retinal detachment.
Methods: Systematic review and meta-analysis looking for all prospective trials and RCTs assessing the accuracy of POCUS for identifying retinal detachment.
Results: 11 studies (n = 844) were identified. Overall, ultrasound was 94.2% (95% CI 78.4% to 98.6%) sensitive and 96.3% (95% CI 89.2% to 98.8%) specific for the diagnosis of retinal detachment with a positive likelihood ratio of 25.2 (95% CI 8.1 to 78.0) and a negative likelihood ratio of 0.06 (95% CI = 0.01 to 0.25).
Conclusions: POCUS is sensitive and specific for the diagnosis of retinal detachment.

Visual acuity is the "vital sign" of the eyes and should ALWAYS be assessed and documented in both eyes when a patient presents to the ED with an ophthalmologic complaint

Dilating pupils for examination

1st drop	2nd drop	Notes
cyclopentolate 1%	phenylephrine 2.5%	can add 2nd trop of phenylephrine if not adequare diation
tropicamide 1%	phenylephrine 2.5%	

Dermatologic Emergencies

Rash Characteristics

A. Diffuse Rashes

- Staphylococcal Scalded Skin Syndrome (SSSS)
  - caused by an exotoxin from infecting strain of coagulase-positive *S. aureus*
  - mostly occurs in children
  - prodrome: fever, irritability, malaise, and skin tenderness
  - sudden onset of diffuse erythema: skin is red, warm, and very tender
  - flaccid bullae that are difficult to see, then desquamate in large sheets
- Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
  - see Dermatology, D26
  - caused by drugs (e.g. phenytoin, sulfas, penicillins, and NSAIDs), bone marrow transplantation, and blood product transfusions
  - usually occurs in adults
  - diffuse erythema followed by necrosis
  - severe mucous membrane blistering
  - entire epidermis desquamation
  - high mortality (>50%)

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
  - see Dermatology, D25
  - presents 1-6 weeks after first exposure to drug; persists wk after withdrawal of drug
  - morbilliform rash involving face, trunk, arms
  - systemic features: fever, malaise, cervical lymphadenopathy, internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- Toxic Shock Syndrome (TSS)
  - see Infectious Diseases, ID22
  - caused by superantigen from *S. aureus* or Group A *Streptococcus*(GAS) activating T-cells and cytokines
  - patient often presents with onset of shock and multi-organ failure, fever
  - diffuse erythematous macular rash
  - at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, and skin (necrotizing fasciitis, gangrene)
  - vesiculobullous lesions
- Erythema Multiforme (EM)
  - commonly caused by herpes simplex; less common: *Mycoplasma pneumoniae*, drug-induced
  - viral prodrome 1-14 d before rash
  - target lesion: central grey bulla or wheal surrounded by concentric rings of erythema and normal skin
  - if mucous membrane involvement, then may have difficulty with oral intake

B. Discrete Lesions

- Pyoderma Gangrenosum
  - unclear pathogenesis: may be due to neutrophil dysfunction, genetic predisposition, or immune dysregulation
  - often associated with IBD, rheumatoid conditions, leukemia, and monoclonal gammopathies
  - often occurs in arms, hands, feet, or perineal region
  - usually begins as painless macule/vesicle/pustule/bulla on red/blue base sloughing, leaving a gangrenous ulcer
- Disseminated Gonococcal Infection (DGI)
  - see Dermatology, D38
  - fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), and septic arthritis (in larger joints, such as knees, ankles, and elbows)
  - most commonly in gonococcus-positive women during menstruation or pregnancy
  - skin lesions usually appear in extremities and resolve quickly (<7 d)
- Meningococcemia
  - Gram-negative bacterium *Neisseria meningitidis* causes flu-like symptoms of headache, myalgia, N/V
  - petechial, macular, or maculopapular lesions with grey vesicular centres
  - usually a few millimeters in size, but may become confluent and hemorrhagic
  - usually appear in extremities, but may appear anywhere
  - look for signs of meningeal irritation: positive jolt accentuation test, Brudzinski, Kernig

History and Physical Exam

- determine onset, course, and location of skin lesions
- fever, joint pain
- associated symptoms: CNS, respiratory, GU, GI, renal, liver, mucous membranes
- medications, sexual encounters, living environment, occupational exposures
- vitals, physical exam based on relevant history

Investigations

- case-dependent, consider: CBC, electrolytes, Cr, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)

Thorough dermatologic examinations are required; examination of asymptomatic skin may identify more lesions; ensure adequate draping during dermatologic examinations

Management

- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevent infection
- if patient unstable, immediately consult for admission: dermatology, or infectious diseases, allergy/immunology, plastic surgery
- specific management is determined by etiology
  - SSSS, TSS, DGI, and meningococcemia
    - IV antibiotics
  - EM, SJS, TEN, and DRESS syndrome
    - stop precipitating medication
    - fluids
    - symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IV immunoglobulin (IVIG), plasmapheresis
    - TEN: debride necrotic tissue
    - EM: treat underlying cause, provide supportive care, and manage symptoms; may need admission for hydration, diffuse lesions, or ocular involvement

SJS = <10% of BSA
SJS/TEN = 10-30% BSA
TEN = >30% BSA

Disposition

- most cases will require urgent care and hospitalization
- SJS & TEN: early transfer to burn centre improves outcome

For an approach to describing a rash and common skin lesions that are seen in the emergency department, refer to Dermatology

Environmental Injuries

Heat Exhaustion and Heat Stroke

HEAT EXHAUSTION

- clinical features relate to loss of circulating volume caused by exposure to heat stress
- "water depletion": heat exhaustion occurs if lost fluid not adequately replaced
- "salt depletion": heat exhaustion occurs when losses replaced with hypotonic fluid

Heat exhaustion may closely resemble heat stroke; heat exhaustion may eventually progress to heat stroke, so if diagnosis is uncertain treat as heat stroke

HEAT STROKE

- life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
- divided into classical and exertional subtypes
- if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, infections), adverse drug events (including drug interactions)

Table 28. Heat Exhaustion vs. Heat Stroke

	Heat Exhaustion	Classical Heat Stroke	Exertional Heat Stroke
Clinical Features	Non-specific malaise, nausea, headache, fatigue Body temperature <40.5°C (usually normal) No coma or seizures Dehydration (HR, orthostatic hypotension)	Occurs in setting of high ambient temperatures (e.g. heat wave, poor ventilation) Often patients are older and sedentary or immobile Dry, hot skin Temp usually >40.5°C Altered mental status, seizures, delirium, or coma May have elevated AST, ALT	Occurs with high endogenous heat production (e.g. exercise) that overwhelms homeostatic mechanisms Patients often younger, more active Skin often diaphoretic Other features as for classical heat stroke, but may also have DIC, acute renal failure, rhabdomyolysis, marked lactic acidosis
Treatment	Rest in a cool environment IV NS if orthostatic hypotension; otherwise replace losses slowly PO with salt and electrolyte solutions	Cool body temperature with water mist (e.g. spray bottle) and standing fans Ice water immersion also effective; monitor body temperature closely using rectal thermometer to avoid hypothermic overshoot Secure airway because of seizure and aspiration risk Give fluid resuscitation if still hypotensive after above therapy Avoid β-agonists (e.g. epinephrine), peripheral vasoconstriction, and antipyretics (e.g. ASA)	

Hypothermia and Cold Injuries

HYPOTHERMIA

- hypothermia is defined as a core temperature below 35°C, in which the body's heat loss is greater than heat production
- etiology: increased heat loss (e.g. environmental exposure), decreased heat production (e.g. endocrine disease), impaired regulation (e.g. CNS failure)
- predisposing risk factors: ethanol use, homelessness, psychiatric disease, and older age (older adults have increased risk due to decreased physiological reserve, chronic diseases, medication side effects, and social isolation)
- treatment based on re-warming and supporting cardiorespiratory function
- complications: coagulopathy, acidosis, dysrhythmias (AFib, VFib, profound bradycardia, asystole), and volume/electrolyte depletion
- labs: CBC, electrolytes, VBG, serum glucose, Cr/BUN, Mg^{2+}, Ca^{2+}, amylase, coagulation profile, troponin, lactate ± β-hCG
- imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- monitors: ECG, initial rectal thermometer followed by transesophageal temperature probe for ongoing monitoring, Foley catheter, NG tube, monitor metabolic status frequently

Table 29. Classification of Hypothermia

Class	Temp	Symptoms/Signs
Mild	32-34.9°C	Tachypnea, tachycardia, ataxia, dysarthria, shivering
Moderate	28-31.9°C	Loss of shivering, dysrhythmias, Osborne (J) waves on ECG, decreased LOC, combative behaviour, muscle rigidity, dilated pupils
Severe	<28°C	Unresponsive, hypotension, acidemia, VFib, AFib, asystole, flaccidity, apnea

Re-warming Options

- gentle fluid and electrolyte replacement in all (due to cold diuresis)
- passive external re-warming
  - suitable for most stable patients with core temperature >32.2°C
  - remove all wet clothes, then cover patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
- active external re-warming
  - involves use of warming blankets
  - beware of "afterdrop" phenomenon
  - safer when done in conjunction with active core re-warming

Afterdrop Phenomenon
Warming of extremities causes vasodilation and movement of cool pooled blood from extremities to core, resulting in a drop in core temperature leading to cardiac arrest

- active core re-warming
  - generally for patients with core temperature <32.2°C, and/or with cardiovascular instability
  - avoids "afterdrop" seen with active external re-warming alone
  - re-warm core by using
    - warmed humidified oxygen, IV fluids
    - peritoneal dialysis with warm fluids
    - gastric/colonic/pleural/bladder irrigation with warm fluids
    - external circulation (ECMO) is most effective and fastest

Approach to Cardiac Arrest in the Hypothermic Patient

- treatment focus: active core re-warming (preferably with extracorporeal membrane oxygenation, ECMO, over cardiopulmonary bypass)
- intubate if required, ventilate with warmed, humidified O_2
- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 min; may have profound bradycardia
- if any pulse at all (even very slow) do NOT do CPR
- if in VFib try to defibrillate up to maximum 3 shocks if core temperature <30°C
- intubate if required, ventilate with warmed, humidified O_2
- medications (vasopressors, antidysrhythmics) may not be effective at low temperatures (controversial); may try one dose
- focus of treatment is re-warming

FROSTBITE

Classification

- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
- 1st degree
  - symptoms: initial paresthesia, pruritus
  - signs: erythema, edema, hyperemia, no blisters
- 2nd degree
  - symptoms: numbness
  - signs: blistering (clear), erythema, edema
- 3rd degree
  - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
  - signs: hemorrhagic blisters, skin necrosis, edema, no movement
- 4th degree
  - extension into subcuticular, osseous, and muscle tissues

Management

- treat for hypothermia: O_2, IV fluids, maintenance of body warmth
- remove wet and constrictive clothing
- immerse in 40-42°C agitated water for 10-30 min (very painful; administer adequate analgesia)
- clean injured area and leave it open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin
- tetanus prophylaxis
- consider antibiotics as frostbite injury has high-risk of infection
- surgical intervention may be required to release restrictive eschars (compartment syndrome)
- never allow a thawed area to re-chill/freeze
- consider using tPA and/or iloprost for severe burns, in conjunction with specialist advice

Burns

- see Plastic Surgery, PL18

Clinical Features/Physical Exam Findings

- burn size
  - rule of nines; does not include 1st degree (superficial) burns
- burn depth
  - superficial (1st degree): epidermis only (e.g. sunburn), painful and tender to palpation
  - superficial partial thickness (2nd degree): extends to epidermis and superficial dermis, blister formation occurs, very painful
  - deep partial thickness (2nd degree): involves hair follicles, sebaceous glands; skin is blistered, exposed dermis is white to yellow, absent sensation
  - full thickness (3rd degree): epidermis and all dermal layers; skin is pale, insensate, and charred or leathery
  - deep (4th degree): involvement of fat, muscle, even bone

Management

- remove noxious agent/stop burning process and consider appropriate PPE usage
- establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury or signs of significant upper airway burns)
- resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)
- fluid boluses if unstable
  - Parkland Formula: Ringer's lactate 4 cc/kg/% BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
  - urine output is best measure of resuscitation, should be 40-50 cc/h or 0.5 cc/kg/h; avoid diuretics

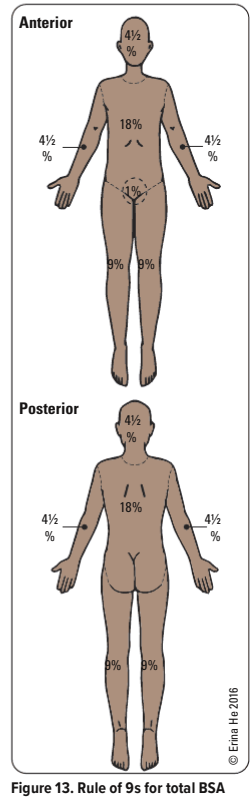


Figure 13. Rule of 9s for total BSA

BSA percentages differ in pediatric patients (e.g., infants have proportionately larger heads).

- pain relief: continuous opioid (e.g. hydromorphone, fentanyl, morphine) infusion for pain with breakthrough doses PRN
- investigations: CBC, electrolytes, U/A, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, burn victims are highly susceptible to infection (portal of entry with reduced immune function) – systemic antibiotics are often required
- tetanus prophylaxis if burn is deeper than superficial dermis

Use palm of the patient's hand to estimate 1% of BSA affected

Disposition

- admit
  - 2nd degree burns >10% BSA, or any significant 3rd degree burns
  - 2nd degree burns on face, hands, feet, perineum, or across major joints
  - electrical, chemical burns, and inhalation injury
  - burn victims with chronic medical conditions or immunosuppressed patients

Burn Causes
- Thermal (flame, scald)
- Chemical
- Radiation (UV, medical/therapeutic)
- Electrical

Inhalation Injury

Etiology

- carbon monoxide (CO) or cyanide (poisoning through dermal contact or inhalation)
- direct thermal injury: limited to upper airway (above the vocal cords)
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

Always look for inhalational injury in patients with burns. Intubate early (prior to fluid boluses) if you suspect inhalation injury, as airway can become obstructed due to edema

History and Physical Exam

- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin and bitter almond odour are classic findings of cyanide toxicity but are often not present clinically
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO_2 normal but O_2 saturation low suggests CO poisoning

Investigations

- CBC, electrolytes, lactate (if high, cyanide toxicity should be assumed)
- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± outpatient bronchoscopy

Management

- CO poisoning: 100% O_2 ± hyperbaric O_2 (controversial, specific scenarios where it can be considered)
- cyanide poisoning: hydroxocobalamin 70 mg/kg IV over 15 min (max 5 g), up to two doses, hemodynamic support; obtain labs immediately as hydroxocobalamin will alter lab test results
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators, and mucolytics (N-acetylcysteine)

Bites

MAMMALIAN BITES

- see Plastic Surgery, PL11

History

- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, risk of rabies exposure/transmission, HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, "fight bites"

Physical Exam

- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status, joints (if applicable)

Investigations

- if bony injury or infection suspected, check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds ± CT to rule out cranial perforation
- ultrasound may be helpful for identifying abscess formation as well as locating radiolucent foreign bodies in infected wounds

Initial Management

- wound cleaning and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
- culture wound if signs of infection (erythema, necrosis, or pus); obtain anaerobic cultures if wound is foul smelling, necrotizing, or if abscess is present; notify lab that sample is from bite wound

- suturing
  - vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  - consider suturing uncomplicated wounds that have been well irrigated/debrided and are vascular
  - provide antibiotics if suturing, and in the case of hand injuries (even if not suturing)
- tetanus immunization if >5 yr or incomplete primary series (see *Table 11, ER17*)

Prophylactic Antibiotics

- types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
- a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present
- dog and cat bites (pathogens: *Pasteurella multocida, S. aureus, S. viridans*)
  - 10-50% of cat bites, and 5% of dog bites become infected
  - 1st line: amoxicillin + clavulanic acid (not cefalexin as it does not cover *Pasteurella* spp. or *Eikenella corrodens*)
- human bites (pathogens: *Eikenella corrodens, S. aureus, S. viridans*, oral anaerobes)
  - carry out a risk assessment for blood borne infections
  - if hand injury, always consider the associated metacarpophalangeal joint
  - 1st line: amoxicillin + clavulanic acid
- rabies (see Infectious Diseases, ID19)
  - reservoirs: warm-blooded animals except rodents (primarily bats and raccoons in Canada), lagomorphs (e.g. rabbits); incidence in domestic animals is low, higher risk if animal bite outside of Canada
  - post-exposure vaccine is effective; treatment depends on local prevalence, solicit guidance from local public health unit

Non-Fatal Drowning

- most common in children <4 yr and teenagers
- causes lung damage, hypoxemia, and may lead to hypoxic encephalopathy
- must also assess for shock, C-spine injuries, hypothermia, and scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

Physical Exam

- ABCs, vitals: watch closely for hypotension
- respiratory: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVS: murmurs, dysrhythmias, JVP (CHF, pneumothorax)
- H&N: assess for C-spine injuries
- neurological: GCS or AVPU, pupils, focal deficits

Investigations

- labs: CBC, electrolytes, ABGs, Cr, BUN
- imaging: CXR (pulmonary edema, pneumothorax) ± C-spine imaging
- ECG

Management

- ABCs, treat for trauma, shock, hypothermia
- cardiac and O_2 monitors, IV access
- intensive respiratory care
  - ventilator assistance if decreased respirations, pCO_2 >50 mmHg, or pO_2 <60 mmHg on maximum FiO_2
  - may require intubation for airway protection, ventilation, pulmonary toilet
  - high flow O_2/CPAP/Bi-PAP may be adequate but some may need mechanical ventilation with positive end-expiratory pressure
- dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, and acidosis
- vomiting: very common, NG suction to avoid aspiration
- convulsions: usually respond to O_2; if not, lorazepam 4 mg IV slowly
- bronchospasm: bronchodilators
- bacterial pneumonia: prophylactic antibiotics not necessary unless contaminated water or hot tub (*Pseudomonas*)
- always provide rescue ventilation and initiate CPR in drowning-induced cardiac arrest even if patient is hypothermic; continue CPR until patient is fully rewarmed

Disposition

- if asymptomatic, may discharge if no respiratory impairment, normal vitals, and normal mentation
- if symptomatic but never hypoxemic, may be discharged after 6-8 h observation period if resolving symptoms, normal vitals, and normal mentation
- CXR should only be considered for an abnormal lung examination or oxygen saturation
- CNS symptoms or hypoxemia: admit
- severe hypoxemia, decreased LOC: ICU

Toxicology

Approach to the Overdose Patient

Indications to Suspect Overdose
Altered LOC/coma
Young patient with life-threatening dysrhythmia
Trauma patient
Bizarre or puzzling clinical feature

History
- age, weight, underlying medical problems, medications
- substance, route, and quantity
- time and symptoms since exposure determines prognosis and need for decontamination
- route
- intention, suicidality

Physical Exam
- focus on: ABCs, LOC/GCS, vitals, pupils

"ABCD3EFG" of Toxicology

- basic axiom of care is symptomatic and supportive treatment
- address underlying problem only once patient is stable

Principles of Toxicology
4 principles to consider with all ingestions:
- Resuscitation (ABCD3EFG)
- Screening (toxidrome, clinical clues)
- Decrease absorption of drug
- Increase elimination of drug

A	**A**irway (consider stabilizing C-spine)
B	**B**reathing
C	**C**irculation
D1	**D**rugs – ACLS as necessary to resuscitate the patient – universal antidotes (DONT)
D2	**D**raw bloods
D3	**D**econtamination (decrease absorption)
E	**E**xpose (look for specific toxidromes)/examine the patient
F	**F**ull vitals, ECG monitor, foley, x-rays
G	**G**ive specific antidotes and treatments

Further Steps following ABCD3EFG
- reassess
- call Poison Information Centre
- obtain corroborative history from family and bystanders

D1 – Universal Antidotes

- treatments that will not harm patients and may be essential

Universal Antidotes

DONT
Dextrose
Oxygen
Naloxone
Thiamine (must give BEFORE dextrose)

Dextrose (glucose)
- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: D50W 0.5-1.0 g/kg (1-2 mL/kg) IV
- children: D25W 0.25 g/kg (2-4 mL/kg) IV

Oxygen
- do not deprive a hypoxic patient of oxygen regardless of the antecedent medical history (i.e. even COPD with CO_2 retention)
- if depression of hypoxic drive, intubate and ventilate

Naloxone (central μ-receptor competitive antagonist, shorter half-life than naltrexone)
- antidote for opioids: administration is both diagnostic and therapeutic (<1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    - response to naloxone can be drastic, so stepwise delivery is recommended
    - 0.05 or 0.1 mg IV with escalation of doses PRN
    - naloxone administration during cardiac arrest:
      - begin ACLS protocol and administer 2 mg IV/IM every 3 min, may increase dose by doubling up to maximum of 12 mg
  - child
    - 0.01 mg/kg initial bolus IV/IO/ETT (max 2 mg per dose)
    - children over 20 kg can receive naloxone 2 mg IV
  - maintenance dose
    - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
    - hourly infusion rate at 2/3 of initial dose that allowed patient to be roused

Although doses in the ED are generally small, administration of naloxone can cause acute opioid withdrawal in people who are chronic opioid users (Ultrarapid Opioid Detoxification, UROD):
Minor withdrawal may present as lacrimation, restlessness, rhinorrhea, diaphoresis, yawning, piloerection, HTN, myalgia, N/V, tachycardia
Severe withdrawal may present as hot and cold flashes, arthralgias, myalgias, N/V, and abdominal cramps

Thiamine (Vitamin B1)

- 200 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke's encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke's encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine is unavailable
- must assume all undifferentiated comatose patients are at risk

Thiamine is deficient in the malnourished. Consider in patients with alcohol use disorder, anorexia, or malnutrition states

D2 – Draw Bloods

- essential tests
  - CBC, electrolytes, BUN/Cr, glucose, INR/PTT, osmolality
  - ABGs, O_2 sat
  - ASA, acetaminophen, EtOH levels
- potentially useful tests
  - drug levels – this is NOT a serum drug screen (e.g. digoxin, iron)
  - Ca^{2+}, Mg^{2+}, PO_4^{3-}
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical features

Urine drug screen is costly and generally not helpful in the ED management of the poisoned patient unless suspicion of ASA, acetaminophen, or toxic EtOH ingestion

Serum Drug Levels

- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only; not often thought to change management)

Table 30. Toxic Gaps (see Nephrology, NP18)

METABOLIC ACIDOSIS

Increased AG: "GOLDMARK" (* = toxic)
Glycols* (ethylene glycol, propylene glycol)
Oxoproline (metabolite of acetaminophen)*
L-lactate
D-lactate (acetaminophen, short bowel syndrome, propylene glycol infusions for lorazepam & phenobarbital)
Methanol*
ASA*
Renal failure
Ketoacidosis (DKA, EtOH*, starvation)

Increased osmolar gap: "MAE DIE" (if it ends in "-ol", it will likely increase the osmolar gap)
Methanol
Acetone
Ethanol
Diuretics (glycerol, mannitol, sorbitol)
Isopropanol
Ethylene glycol

Note: normal osmolar gap does not rule out toxic alcohol; only an elevated gap is helpful

Decreased AG
Electrolyte imbalance (increased Na^+ /K /Mg^{2+})
Hypoalbuminemia (50% fall in albumin ~5.5 mmol/L decrease in the AG)
Lithium, bromine elevation
Paraproteins (multiple myeloma)

Increased O_2 saturation gap
Carboxyhemoglobin
Methemoglobin
Sulfmethemoglobin

Normal AG
Renal HCO_3^- loss: renal tubular acidosis, hyperparathyroidism
GI HCO_3^- loss: diarrhea, fistula
Other: NS infusion, acetazolamide, hyperkalemia, hypoaldosteronism

Table 31. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

Test	Finding	Selected Causes
ABG	Hypoventilation (high pCO_2) Hyperventilation (low pCO_2)	CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, EtOH) Salicylates, CO, other asphyxiants
Electrolytes	AG metabolic acidosis Hyperkalemia Hypokalemia	**"GOLDMARK"**: see Table 30 Digitalis glycosides, fluoride, potassium Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin
Glucose	Hypoglycemia	Oral hypoglycemic agents, insulin, EtOH, ASA
Osmolality and Osmolar Gap	Elevated osmolar gap	**"MAE DIE"**: see Table 30
ECG	Wide QRS complex Prolonged QT interval Atrioventricular block	TCAs, quinidine, other class Ia and Ic antidysrhythmic agents Terfenadine, astemizole, antipsychotics, hydroxychloroquine Ca^{2+} antagonists, digitalis glycosides, phenylpropanolamine, hydroxychloroquine
Abdominal X-Ray	Radiopaque pills or objects	**"CHIPES"**: Calcium, Chloral hydrate, CCl_4, Heavy metals, Iron, Potassium, Enteric coated Salicylates, and some foreign bodies
Serum Acetaminophen	Elevated level (1000 µmol/L 4 h after ingestion) Consult Rumack-Matthew nomogram in single ingestion cases	May be only sign of acetaminophen poisoning

Anion Gap
= $Na^+ – Cl^- – HCO_3^-$
Normal AG ≤12 mM/L

Osmolar Gap
= [(2 x Na^+) + Glu + Urea] - Measured Osmolality
Normal <10

D3 – Decontamination and Enhanced Elimination

Ocular Decontamination
- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

Dermal Decontamination
- wear protective gear
- remove clothing, brush off toxic agents, irrigate all external surfaces

Gastrointestinal Decontamination
- single dose activated charcoal
  - use of activated charcoal is a source of much debate amongst toxicologists, evidence of effectiveness is not strong and risk of aspiration is high
  - consider if recent ingestion, delayed absorption medication, can consult poison control PRN
  - adsorption of drug/toxin to activated charcoal decreases toxin bioavailability
  - contraindications: unprotected airway, late presentation after ingestion (1-2 h post ingestion), small bowel obstruction, poor toxin adsorption
  - dose: 10 g/g drug ingested or 1 g/kg body weight (may vary depending on ingestion)
  - odourless, tasteless, prepared as slurry with H_2O
- whole bowel irrigation (occasionally used)
  - 500 mL/h (child) to 2000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
    - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated
  - indications
    - awake, alert, can be nursed upright, with an NG tube who cannot tolerate drinking it, or intubated and airway protected
    - delayed release product
    - drug/toxin not bound to charcoal
    - drug packages (if any evidence of breakage emergency surgery)
    - recent toxin ingestion
  - contraindications
    - evidence of ileus, perforation, or obstruction
- multidose activated charcoal
  - may be used for: carbamazepine, phenobarbital, quinine, theophylline, for toxins which undergo enterohepatic recirculation
  - removes drug that has already been absorbed by drawing it back into GI tract
  - various regimens: 12.5 g (1/4 bottle) PO q1 h or 25 g (1/2 bottle) PO q2 h until non-toxic
- surgical removal in extreme cases
  - surgical indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
- use of cathartics (i.e. ipecac) and gastric lavage in the ED is generally not recommended

Lipid Emulsification
- new therapy used in cardiogenic shock due to toxins
- may be used for: anesthetics (e.g. lidocaine), β-blocker/calcium channel blocker, atypical antidepressant overdose
- initial bolus lipid solution 20% 1.5 mL/kg over 3 min then infusion of 0.25 mL/kg/min

Urine Alkalinization
- may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
- weakly acidic substances can be trapped in alkaline urine (pH >7.5) to increase elimination

Hemodialysis
- indications/criteria for hemodialysis
  - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution, or rapid plasma equilibration
  - clinical deterioration despite maximal medical support
- useful for the following toxins
  - methanol
  - ethylene glycol
  - salicylates
  - lithium
  - phenobarbital
  - chloral hydrate (trichloroethanol)
- others include theophylline, carbamazepine, valproate, methotrexate

E – Expose and Examine the Patient

- vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours, and CNS
- head-to-toe survey including
  - C-spine
  - signs of trauma, seizures (incontinence, "tongue biting," etc.), infection (meningismus), or chronic alcohol/drug misuse (track marks, nasal septum erosion)
  - feel the patient's axillae; in the average patient, should be somewhat moist (if dry, may indicate anticholinergic toxicity)
- mental status

Table 32. Specific Toxidromes

Toxidrome	Overdose Signs and Symptoms		Examples of Drugs
Anticholinergic	Hyperthermia Dilated pupils Dry skin Vasodilation Agitation/hallucinations Ileus Urinary retention Tachycardia	"Hot as a hare" "Blind as a bat" "Dry as a bone" "Red as a beet" "Mad as a hatter" "The bowel and bladder lose their tone and the heart goes on alone"	Antidepressants (e.g. TCAs) Cyclobenzaprine (Flexeril®) Carbamazepine Antihistamines (e.g. diphenhydramine) Antiparkinsonians Antipsychotics Antispasmodics Belladonna alkaloids (e.g. atropine)
Cholinergic	**"DUMBELS"** **D**iaphoresis, Diarrhea, Decreased BP **U**rination **M**iosis **B**ronchospasm, **B**ronchorrhea, **B**radycardia **E**mesis, **E**xcitation of skeletal muscle **L**acrimation **S**alivation, **S**eizures		Natural plants: mushrooms, trumpet flower Anticholinesterases: physostigmine Insecticides (organophosphates, carbamates) Nerve gases
Extrapyramidal	Dysphonia, dysphagia Rigidity and tremor Motor restlessness, crawling sensation (akathisia) Constant movements (dyskinesia) Dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis)		Major tranquilizers Antipsychotics
Hemoglobin Derangements	Increased respiratory rate Decreased LOC Seizures Cyanosis unresponsive to O_2 Lactic acidosis		CO poisoning (carboxyhemoglobin) Drug ingestion (methemoglobin, sulfmethemoglobin)
Opioid, Sedative/ Hypnotic, EtOH	Hypothermia Hypotension Respiratory depression (opioid) Dilated or constricted pupils (pinpoint in opioid) CNS depression		EtOH Benzodiazepines Opioids (morphine, heroin, fentanyl, etc.) Barbiturates GHB ("G," "liquid gold")
Sympathomimetic	Increased temperature CNS excitation (including seizures) Tachycardia, HTN N/V Diaphoresis Dilated pupils		Amphetamines, caffeine, cocaine, LSD, phencyclidine Ephedrine and other decongestants Thyroid hormone Sedative or EtOH withdrawal
Serotonin Syndrome	Mental status changes, autonomic hyperactivity, neuromuscular hyperactivity, hyperthermia, diarrhea, HTN		MAOI, TCA, SSRI, opiate analgesics Cough medicine, weight reduction medications

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

F – Full Vitals, ECG Monitor, Foley, X-Rays

G – Give Specific Antidotes and Treatments

Urine Alkalinization Treatment for ASA Overdose

- urine pH >7.5
- fluid resuscitate first, then 3 amps $NaHCO_3$/L of D5W at 1.5x maintenance
- add 20-40 mEq/L KCl if patient is able to urinate

Table 33. Protocol for Warfarin Overdose

INR	**Management:** Consider Prothrombin Complex Concentrate (Octaplex®, Beriplex®) for any elevated INR, AND either life-threatening bleeding, or a plan for the patient to undergo a surgical procedure within the next 6 h (vitamin K takes 4-6 h post IV administration to work)
<5.0	Cessation of warfarin administration, observation, serial INR/PT
5.1–9.0	If no risk factors for bleeding, hold warfarin x1-2 d and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding
9.1–20.0	Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary
>20.0	Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4 h) if needed

Table 34. Specific Antidotes and Treatments for Common Toxins*

Toxin	Treatment	Considerations
Acetaminophen	Decontaminate (activated charcoal) N-acetylcysteine	Often clinically silent; evidence of liver/renal damage delayed >24 h Toxic dose >200 mg/kg (>7.5 g adult) Monitor drug level 4 h post-ingestion; also liver enzymes, INR, PTT, BUN, Cr Hypoglycemia, metabolic acidosis, encephalopathy poor prognosis Dialysis may be required to manage in very high overdoses
Acute Dystonic Reaction	Benztropine: 1-2 mg IM/IV then 2 mg PO 3 d OR Diphenhydramine 1-2 mg/kg IV, then 25 mg PO QID x3 d	Benztropine (Cogentin®) has euphoric effect and the potential for misuse
Anticholinergics	Consider decontamination (activated charcoal) Supportive care	Special antidotes available; consult Poison Information Centre
ASA	Consider decontamination (activated charcoal) Alkalinize urine; want urine pH >7.5	Monitor serum pH and drug levels closely Monitor K^+ level; may require supplement for urine alkalinization Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or end-organ damage (i.e. unable to diurese)
Benzodiazepines	Consider decontamination (activated charcoal) Flumazenil (only use in iatrogenic overdose (operative oversedation) due to extensive contraindications (mixed overdose, Hx of EtOH, seizures)) Supportive care	
β-blockers	Consider decontamination (activated charcoal, consider whole bowel irrigation for extended-release ingestion) IV glucagon, IV calcium chloride, IV high-dose insulin (with dextrose), IV lipid emulsification	
Calcium Channel Blockers	Consider decontamination (activated charcoal, consider whole bowel irrigation for extended-release ingestion) IV glucagon, IV calcium chloride, IV high-dose insulin (with dextrose), IV intralipid	Order ECG, electrolytes (especially Ca^{2+}, Mg^{2+}, Na^+, K^+)
Cocaine	Decontaminate (activated charcoal) if oral Aggressive supportive care	β-blockers are contraindicated in acute cocaine toxicity Intralipid for life-threatening symptoms Consider benzodiazepines for any major side effect of cocaine overdose (agitation, hypertension, tachycardia, etc.)
CO Poisoning	See *Inhalation Injury, ER47* Supportive care 100% O_2; may require hyperbaric O_2	Order ECG, VBG. Consider lactate and troponin depending on specific presentation
Cyanide	Hydroxocobalamin 5 g IV (Cyanokit™)	Consider in all patients found in a fire
Digoxin	Consider decontamination (activated charcoal) Digoxin-specific antibody fragments 10-20 vials IV if acute; 3-6 if chronic 1 vial (40 mg) neutralizes 0.5 mg of toxin	Use for life-threatening dysrhythmias unresponsive to conventional therapy, 6 h serum digoxin >12 nmol/L, initial K^+ >5 mmol/L, ingestion >10 mg (adult)/>4 mg (child) Common dysrhythmias include VFib, VTach, and conduction blocks
Ethanol	Thiamine 100 mg IM/IV Manage airway and circulatory support	Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH Order serum EtOH level and glucose level; treat glucose level appropriately
Ethylene Glycol/ Methanol	Fomepizole (4-methylpyrazole) 15 mg/kg IV load over 30 min, then 10 mg/kg q12 h OR Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h	CBC, electrolytes, glucose, ethanol level Consider hemodialysis
Heparin	Protamine sulfate 25-50 mg IV	For unfractionated heparin overdose only
Insulin IM/SC/ Oral Hypoglycemic	Glucose IV/PO/NG tube Glucagon: 1-2 mg IM (if no access to glucose)	Glyburide carries highest risk of hypoglycemia among oral agents Consider octreotide for oral hypoglycemics (50-100 µg SC q6 h) in these cases; consult local Poison Information Centre
MDMA	Consider decontamination (activated charcoal) Supportive care	Monitor CK; treat rhabdomyolysis with high flow fluids: aggressive external cooling for hyperthermia Review medical history if possible for serotonergic use
Opioids	See *Universal Antidotes, ER49*	
TCAs	Consider decontamination (activated charcoal) Aggressive supportive care $NaHCO_3$ bolus for wide QRS/seizures	Flumazenil antidote contraindicated in combined TCA and benzodiazepine overdose Also consider cardiac and hypotension support, seizure control Intralipid therapy
Organophosphate	100% O_2 + endotracheal intubation Atropine Pralidoxime (2-PAM)	Succinylcholine

* Call local Poison Information Centre for reporting of cases, specific doses, and treatment recommendations. Most toxicology cases should involve communication with your local Poison Information Centre

Alcohol Related Emergencies

• see Psychiatry, PS28

Acute Intoxication

- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia, may progress to coma
- hypotension (peripheral vasodilation)
- if obtunded, rule out
  - head trauma/intracranial hemorrhage
  - associated depressants, toxic alcohols
- may also contribute to respiratory/cardiac depression
  - hypoglycemia (screen with bedside glucometer)
  - hepatic encephalopathy: confusion, altered LOC, coma

Alcohol levels correlate poorly with intoxication

Alcohol intoxication may invalidate informed consent

Withdrawal

- beware of withdrawal signs
- treatment
  - diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1 h (if known liver dysfunction) until two CIWA scores <10
- frequency of dosing may have to be increased depending on clinical response
  - may use CIWA protocol and give benzodiazepines as above until CIWA <10
  - thiamine 200 mg IM/IV then 50-100 mg/d
    - naltrexone & gabapentin if no improvement
  - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  - admit patients with delirium tremens or multiple seizures or persistently high CIWA (symptoms) despite high doses of benzodiazepines

CIWA Withdrawal Symptoms
- N/V
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Visual disturbances
- Tactile disturbances
- Auditory disturbances
- Headache
- Disorientation
- 10 symptoms each scored out of 7 except orientation, which is scored out of 4

Table 35. Alcohol Withdrawal Signs

Time Since Last Drink	Syndrome	Description
6-8 h	Mild withdrawal	Generalized tremor, anxiety, agitation, but no delirium Autonomic hyperactivity (sinus tachycardia), insomnia, N/V
1-2 d	Alcoholic hallucinations	Visual (most common), auditory, and tactile hallucinations Vitals often normal
8 h-2 d	Withdrawal seizures	Typically brief generalized tonic-clonic seizures May have several within a few hours CT head if focal seizures have occurred
3-5 d	DT	5% of untreated withdrawal patients Severely confused state, fluctuating LOC Agitation, insomnia, hallucinations/delusions, tremor Tachycardia, hyperpyrexia, diaphoresis High mortality rate

Cardiovascular Complications

- HTN
- cardiomyopathy: SOB, edema
- dysrhythmias: AFib (most common), atrial flutter, SVT, VTach (especially Torsades if hypomagnesemic/hypokalemic)

Metabolic Abnormalities

- alcoholic ketoacidosis
  - metabolic acidosis, urine ketones, low glucose, and normal osmolality
  - history of chronic alcohol intake with abrupt decrease/cessation
  - malnourished, abdominal pain with N/V
  - treatment: thiamine (250-500 mg IM/IV prior to dextrose), dextrose, volume repletion (with NS or LR)
  - generally resolves in 12-24 h
- toxic alcohols
  - ethylene glycol: CNS, CVS, renal findings
  - methanol
    - early: lethargy, confusion
    - late: headache, visual changes, N/V, abdominal pain, tachypnea
  - toxic alcohols initially produce a high osmolar gap, as the toxic alcohol is metabolized the osmolar gap drops and an anion gap develops leading to a severe metabolic acidosis, the goal of treatment is to block this pathway
  - EtOH co-ingestion is protective

- treatment
  - urgent hemodialysis required
  - fomepizole 15 mg/kg IV bolus (treatment of choice) or 10% EtOH IV bolus and infusion to achieve blood level of 22 mmol/L (EtOH loading may be done PO)
  - consider folic acid for methanol, and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites
- other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

Gastrointestinal Abnormalities

- gastritis
  - common cause of abdominal pain and GI bleed in chronic alcohol users
- pancreatitis
  - Elevated serum lipase is diagnostic
  - hemorrhagic form (15%) associated with increased mortality
  - fluid resuscitation very important
- hepatitis
  - AST/ALT ratio >2 suggests alcohol as the cause
- peritonitis/spontaneous bacterial peritonitis
  - leukocytosis, fever, generalized abdominal pain/tenderness
  - occasionally accompanies cirrhosis
  - paracentesis for diagnosis (common pathogens: *E. coli, Klebsiella, Streptococcus*)
  - albumin shown to improve outcomes in sBP patients
- GI bleeds
  - most commonly gastritis or ulcers, even if patient known to have varices
  - consider Mallory-Weiss tear secondary to retching
  - often complicated by underlying coagulopathies
  - minor: treat with antacids
  - severe or recurrent: endoscopy
  - variceal bleeds: octreotide

Disposition from the Emergency Department

- alcohol
  - before patient leaves ED ensure stable vital signs, can walk unassisted, and fully oriented
  - explore need for social services, housing, addictions services, or detox program
  - ensure patient can obtain any medications prescribed and can complete any necessary follow-up
- methanol, ethylene glycol
  - admit for dialysis
- TCAs
  - prolonged/delayed cardiotoxicity warrants admission to monitored ICU bed
  - if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  - sinus tachycardia alone (most common finding) with history of overdose warrants observation in ED and consultation with poison centre
- hydrocarbons/smoke inhalation
  - pneumonitis may lag 6-8 h
  - consider observation for repeated clinical and radiographic examination
- ASA, acetaminophen
  - if borderline level, get second level 2-4 h after first
  - for ASA, must have at least 2 measurements showing decreasing toxin serum concentration before discharge (3 levels minimum)
- oral hypoglycemics
  - admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  - observe asymptomatic patient for at least 8 h
- opioids
  - administer naloxone, a short-acting opioid antagonist, preferably IV in incremental doses (0.2-1 mg)
  - patients in cardiorespiratory arrest following possible opioid overdose should be given 2 mg of naloxone minimum
  - if a naloxone infusion is needed: admit to ICU; start infusion at 2/3rds of the minimum effective bolus dose (e.g. if the minimum effective dose was 0.3 mg, then the infusion dose should start at 0.2 mg/h)
  - admit and observe for 24 h
  - referral to rapid access clinic and offer a naloxone kit

Psychiatric Consultation

- once patient medically cleared, arrange psychiatric intervention if required
- in the setting of an intentional overdose, patients should be certified using the local mental health legislation
- beware – suicidal ideation may not be expressed

Psychiatric Emergencies

Approach to Common Psychiatric Presentations

- see Psychiatry, PS2
- before seeing patient, ensure your own safety; have security/police available if necessary

History

- safety
  - assess suicidality: suicidal ideation (SI; passive/active), intent, plan, lethal means, past history and family history of attempts, protective factors
    - Use scales, like SAD PERSONS (Scale and Columbia–Suicide Severity Rating Scale), to assess suicide risk
  - assess homicidality: homicidal ideation (HI), access to weapons, intended victim, and history of violence
  - driving and children
  - command hallucinations
- identify current stressors, mood (in patient's own words), and coping strategies
- psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
- substance use history: substance(s), most recent use, amount, previous withdrawal reactions
- past psychiatric history, medications, adherence with medications, admissions
- medical history: obtain collateral if available (patients are unable to provide collateral if experiencing acute psychosis, catatonia, or intoxication)

Key Functions of Emergency Psychiatric Assessment

- Is the patient medically stable?
- Rule out medical cause
- Is psychiatric consult needed?
- Are there safety issues (SI, HI)?
- Is patient certifiable? (must demonstrate risk (present/past test) and apparent mental illness (future test))

Physical Exam

- emphasis on mental status exam: general appearance, behaviour, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability
- complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder; which could be contributing or causing psychiatric presentation

Psychiatric Review of Systems

MOAPS
Mood
Organic
Anxiety
Psychosis
Safety

Investigations

- investigations vary with age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
- as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum Cr, BUN, and osmolality
- blood levels of psychiatric medications
- CT head if suspect neurological etiology
- LP if indicated (anti-NMDA receptor encephalitis)

Acute Psychosis

Differential Diagnosis

- primary psychotic disorder (e.g. schizophrenia)
- secondary to medical condition (e.g. delirium)
- drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
- infectious (CNS)
- metabolic (hypoglycemic, hepatic, renal, thyroid)
- structural (hemorrhage, neoplasm)
  - autoimmune (anti-NMDA receptor encephalitis)

Management

- violence prevention
  - remain calm, empathic, and reassuring
  - ensure safety of staff and patients, have extra staff and/or security on hand
  - patients demonstrating escalating agitation or overt violent behaviour may require physical restraint and chemical restraint
- treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
  - benzodiazepines: lorazepam 2 mg PO/IM/SL
  - antipsychotics: olanzapine 5-10 mg PO/IM, haloperidol 5 mg PO/IM
- treat underlying medical condition
- psychiatry or Crisis Intervention Team consult

Suicidal Patient

Epidemiology

- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr
- significantly increased incidence among marginalized communities, particularly Indigenous peoples and 2SLGBTQQIA+ Canadians

See Psychiatry, *Common Forms*, PS61 for certification (involuntary assessment/admission) considerations

Management
- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), past history and family history of attempts, protective factors
- admit if there is evidence of: active intent and organized plan, access to lethal means, psychiatric disorder, intoxication (in rare circumstances, active suicidal ideation may resolve with few days of abstinence)
- patient may require certification based on local mental health legislation if unwilling to stay voluntarily
- do not start long-term medications in the ED
- psychiatry or Crisis Intervention Team consult

High-Risk Patients

SAD PERSONS
Sex = male
Age >45 yr
Depression
Previous attempts
Ethanol use
Rational thinking loss
Suicide in family
Organized plan
No spouse, no support system
Serious illness

Common Pediatric ED Presentations

Modified Glasgow Coma Score

Table 36. Modified GCS

Modified GCS for Infants		
Eye Opening	**Verbal Response**	**Motor Response**
4 – spontaneously	5 – coos, babbles	6 – normal, spontaneous movement
3 – to speech	4 – irritable cry	5 – withdraws to touch
2 – to pain	3 – cries to pain	4 – withdraws to pain
1 – no response	2 – moans to pain	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response
Modified GCS for Infant (<2 years)1 or Non-verbal Patients		
Eye Opening	**Verbal Response**	**Motor Response**
4 – spontaneously	5 – oriented, social, speaks, interacts	6 – normal, spontaneous movement
3 – to speech	4 – confused speech, disoriented, consolable	5 – localizes to pain
2 – to pain	3 – inappropriate words, not consolable/aware	4 – withdraws to pain
1 – no response	2 – incomprehensible, agitated, restless, not aware	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response

1Consider Alert, Pain, Verbal, Unconscious (AVPU) scale

Any trauma or suspected trauma patient <1 yr with a large, boggy scalp hematoma requires U/S or CT

Respiratory Distress

- see Pediatrics, P80, P93

History and Physical Exam
- see Pediatrics, P4 for how to obtain a standard pediatric history
- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
  - see Pediatrics, P3 for age specific vital signs
- pulsus paradoxus (rarely used clinically)
- wheezing, grunting, vomiting

Table 37. Stridorous Upper Airway Diseases: Differential Diagnosis

Feature	Croup	Bacterial Tracheitis [1]	Epiglottitis [1]
Age Range (yr)	0.5-4	5-10	2-8
Prodrome	Mild for days then acutely severe	Hours to days	Minutes to hours
Temperature	Low grade	High	High
Radiography	Steeple sign [2]	Exudates in trachea [3]	Thumb sign
Etiology	Parainfluenza	*S. aureus*/GAS	*H. influenzae* type b
Barky Cough	Yes	Yes	No
Drooling	Occasionally	No	Yes
Appear Toxic	No	Yes	Yes
Intubation/ICU4	No but yes if severe (rare)	Yes	Yes
Antibiotics	No	Yes	Yes
NOTE	Oral exam	Oral exam	No oral exam, consult ENT

[1]Now rare with Hib vaccine in common use
[2]Rarely perform x-ray unless unresponsive to therapy
[3]Found as diffuse haziness and irregularity of the anterior wall of trachea; consider imaging only after ruling out epiglottitis
[4]Should only be performed by experienced providers; ideally in the OR

Management
- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - dexamethasone x 1 dose
  - assess croup severity (can use Westley score): in moderate croup, child may have stridor and sternal/intercostal indrawing at rest, and moderate difficulty breathing; in severe croup, child has stridor and sternal/intercostal indrawing at rest, and worsening cyanosis over time
  - if moderate-severe, add nebulized or MDI epinephrine (racemic has limited availability)
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
  - humidified O_2 has no evidence for efficacy
- bacterial tracheitis
  - airway maintenance - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g. cloxacillin), pending C&S
- epiglottitis
  - 4 D's: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
  - do not examine oropharynx or agitate patient
  - immediate anesthesia/ENT call – intubate
  - then IV fluids, antibiotics, blood cultures

Febrile Infant and Febrile Seizures

FEBRILE INFANT
- for fever >38°C without obvious focus
  - <28 d
    - admit
    - full septic workup (CBC and differential, CRP, blood C&S, urine C&S, LP ± stool C&S, CXR if indicated)
    - treat empirically with broad spectrum IV antibiotics (ampicillin, and ceftazidime or cefepime or cefotaxime (if available) or gentamicin (add acyclovir or vancomycin when indicated))
  - 28-90 d
    - as above unless infant meets Rochester criteria, if so, complete a partial septic workup (CBC and differential, blood C&S, urine C&S, CXR if indicated)
    - antibiotics (ceftriaxone or cefotaxime (if available), add acyclovir or vancomycin when indicated)
  - >90 d
    - toxic: admit, treat, full septic workup
    - non-toxic and no focus: investigate as indicated by history and physical
    - if bacterial: antibiotics (ceftriaxone or cefotaxime (if available, add acyclovir or vancomycin when indicated)

Rochester Criteria for Febrile Infants Ages 28-90 Days Old
- Helps identify SBI (serious bacterial infection) and guide testing/work-up for well-looking febrile neonates
- Non-toxic looking
- Previously well (>37 wk gestational age, home with mother, no hyperbilirubinemia, no prior antibiotics or hospitalizations, no chronic/underlying illness)
- No skin, soft tissue, bone, joint, or ear infection on physical exam
- WBC 5000-15000, bands <1500, urine <10 WBC/HPF, stool <5 WBC/HPF

FEBRILE SEIZURES
- see Pediatrics, P88

Etiology
- children age 6 mo-6 yr with fever or history of recent fever
- typical vs. atypical febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- well-looking after seizure

Investigations and Management
- if confirmed febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
  - note: may also have fever but may not meet criteria for febrile seizure
- ± EEG (especially if first seizure), head U/S (if fontanelle open)

Table 38. Typical vs. Atypical Febrile Seizures

Characteristic	Typical	Atypical
Duration	<5 min	>5 min
Type of Seizure	Generalized	Focal features
Frequency	1 in 24 h	>1 in 24 h

Abdominal Pain

• see Pediatrics, P47

History
- neuro, infections, autoimmune, hematology, trauma, abuse Hx questions
- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake
  - stress and/or social issues (most common in middle aged children)

Physical Exam
- HEENT, respiratory, abdominal exam, testicular exam

Red Flags for Abdominal Pain
- Significant weight loss or growth retardation (need growth chart)
- Fever
- Joint pain with objective physical findings
- Rash
- Rectal bleeding
- Rebound tenderness and radiation of pain to back, shoulders, or legs
- Pain wakes from sleep
- Severe diarrhea and encopresis

Table 39. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents

Medical	Surgical
Colic	Malrotation with volvulus
UTI	Hirschsprung's disease
Constipation	Necrotizing enterocolitis
Gastroenteritis	Incarcerated hernia
Sepsis	Intussusception
Henoch-Schönlein purpura	Duodenal atresia
IBD	Appendicitis
Hemolytic uremic syndrome	Cholecystitis
Pneumonia	Pancreatitis
Strep throat	Adnexal torsion (testicular or ovarian)
Sickle cell disease crisis	Ectopic pregnancy
DKA	Trauma
Functional	Pyloric stenosis

*Remember to keep an index of suspicion for child abuse

Common Infections

• see Pediatrics, P58

Table 40. Antibiotic Treatment of Pediatric Bacterial Infections

Infection	Pathogens	Treatment
MENINGITIS SEPSIS		
Neonatal	Group B *Streptococcus* (GBS), *E. coli*, *Listeria*, Gram-negative bacilli	ampicillin + cefotaxime
1-3 mo	Same pathogens as above and below	ceftriaxone/cefotaxime + vancomycin + ampicillin (if immunocompromised)
>3 mo	*S. pneumoniae*, *H. influenzae* type B (>5 yr), meningococcus	ceftriaxone + vancomycin
OTITIS MEDIA		
1st Line	*S. pneumoniae*, *H. influenzae* type B, *M. catarrhalis*	amoxicillin 75-90 mg/kg/d BID
1st Line with Penicillin Allergy		1. cefprozil or cefuroxime-axetil 30 mg/kg/d BID/TID OR ceftriaxone 50 mg/kg/dayIM x 3 d (if minor allergy) 2. clarithromycin 15 mg/kg/d BID (for severe allergy); known to have inferior bacterial killing capabilities
Treatment Failure		7:1 amoxicillin to clavulanate ratio ≤35 kg: 45-60 mg/kg/d TID >35 kg: 50 mg PO TID
STREP PHARYNGITIS		
	Group A β-hemolytic *Streptococcus*	penicillin/amoxicillin, cefalexin, or erythromycin (can cause GI upset)
UTI		
	E. coli, *Proteus*, *H. influenzae*, *Pseudomonas*, *S. saprophyticus*, *Enterococcus*, GBS	Oral: cefixime IV: aminoglycoside (gentamicin) ± ampicillin; or use cefotaxime or ceftriaxone
PNEUMONIA		
1-3 mo	Viral, *S. pneumoniae*, *C. trachomatis*, *B. pertussis*, *S. aureus*, *H. influenzae*	IV: ceftriaxone
3 mo-5 yr	Viral, *S. pneumoniae*, *S. aureus*, *H. influenzae*, *Mycoplasma pneumoniae*	if discharged: amoxicillin or cefprozil if admitted: ceftriaxone
>5 yr	As above	ampicillin/amoxicillin OR cefuroxime

Child Abuse and Neglect

- see Pediatrics, P18
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - HI: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken baby syndrome: diffuse brain injury, subdural/SAH, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures <1 yr, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - GU/GI injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea

Association of 2 Social Needs Interventions with Child Emergency Department Use and Hospitalizations
JAMA Pediatr 2022;176:716-717
Purpose: To link social needs interventions to healthcare outcomes among pediatric populations.
Methods: 604 child-caregiver pairs were randomized to groups in which they are given a social resources handout (SRH) with and without the help of a patient navigator (PN) support.
Results: During the 90 d of follow-up, pairs that navigated the SRH alone were associated with increased probability of hospitalization when compared to those given professional help (HR 5.69; 95% CI, 1.07-30.10; p = 0.04).
Conclusion: Social interventions, such as SRH plus PN guidance, can lead to improved pediatric health care outcomes in the ED.

Presentation of Neglect

Failure to thrive, developmental delay

Inadequate or dirty clothing, poor hygiene

Child exhibits poor attachment to parents

Procedures that may Require Sedation

- Setting fractures
- Reducing dislocations
- Draining abscesses
- Exploring wounds/ulcers/superficial infections
- Endoscopic examination
- Reduce patient anxiety/agitation for imaging/procedures

Common Medications

Table 41. Commonly Used Medications

Drug	Dosing Schedule	Indications	Comments
Acetaminophen	325-650 mg PO q4-6h PRN	Pain control	Max 4 g daily
Activated charcoal	30-100 g PO in 250 mL H_2O	Poisoning/overdose	Efficacy and safety are case-dependent and are a source of debate
ASA	325-650 mg PO q4 h max 4 g/d stroke/MI risk: 81-325 mg PO once daily 160 mg chewed	Pain control Prevention of adverse cardiac events ACS	
β-blockers (metoprolol)	5 mg slow IV q5 min x3 if no contraindications Or 25 mg PO BID up to 100 mg PO BID	Rate control in AFib	
Diazepam	anxiety: 2-10 mg PO TID/QID alcohol withdrawal: 10-20 mg PO/IV q1 h titrated to signs/symptoms	Anxiety Alcohol withdrawal	
Enoxaparin	1 mg/kg SC BID	Acute MI DVT Prophylaxis/treatment PE or DVT in patients who cannot take DOACs	
Epinephrine	anaphylaxis: 0.3-0.5 mg IM; ACLS cardiac arrest: 1 mg IV q3-5 min ACLS bradycardia: 2-10 µg/min IV infusion	Anaphylaxis, ACLS cardiac arrest, ACLS bradycardia Hypotension	Max 1 mg/dose
Fentanyl	0.5-1.0 µg/kg IV	Procedural sedation Pain control	Very short acting narcotic (complication=apnea)
Furosemide (Lasix®)	CHF: 40-80 mg IV HTN: 10-40 mg PO BID	CHF HTN	Monitor for electrolyte imbalances; also risk of ototoxicity with high dose
Glucose	0.5-1.0 g/kg (1-2 mL/kg) IV of D50W	Hypoglycemia/DKA	In conjunction with Insulin for hyperkalemia
Haloperidol	2.5-5.0 mg PO/IM initial effective dose 6-20 mg/d	Psychosis Cannabis Hyperemesis Syndrome (any N/V) Sedation	Monitor for side effects if prescribing to a patient with Parkinson's disease (extrapyramidal side effects); results in CNS depression
Ibuprofen	200-800 mg PO TID PRN max 1200 mg/d	Mild to moderate acute pain Analgesic and anti-inflammatory properties	
Insulin	bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per h	Hyperglycemia CCB/BB overdose	Monitor blood glucose levels Consider K+ replacement, also measure blood glucose levels before administration
Ipratropium bromide	2-3 puffs inhaled TID-QID, max 12 puffs/d	Asthma COPD	Contraindications include: peanut/soy allergy Caution with narrow-angle glaucoma
Lidocaine with epi	max 7 mg/kg SC	Local anesthetic	
Lidocaine w/o epi	max 5 mg/kg SC	Local anesthetic	
Lorazepam	anxiety: 0.5-2 mg PO/IM/IV q6-8 h status epilepticus: 4 mg IV repeat up to q5 min	Anxiety Status epilepticus Alcohol withdrawal	

Table 41. Commonly Used Medications

Drug	Dosing Schedule	Indications	Comments
Midazolam	50 µg/kg IV	Procedural sedation Sedation for agitation	Short acting benzodiazepine (complication = apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation
Morphine	0.05-0.1 mg/kg	Mild to moderate acute/chronic pain Prescribed in combination with NSAIDs or acetaminophen	GI and constipation side effects DO NOT CRUSH, CUT, or CHEW (increases risk of overdose) Risk of tolerance
Naloxone	0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg	Comatose patient Opioid overdose Reversal in procedural sedation	If patient is a chronic opioid user begin with very small doses, and go up with small increments as needed
Nitroglycerin	acute angina: 0.3-0.6 mg SL q5 min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5 min	Angina Acute MI (for symptomatic control only) Heart failure	Not to be used with other antihypertensives Not in right ventricular MI
Percocet 10/325®	1-2 tabs PO q6 h PRN	Moderate pain control	Oxycodone + acetaminophen Max 4 g acetaminophen daily
Phenytoin	Status epilepticus: *see Table 17, ER26*	Status epilepticus Epilepsy	Begin maintenance dose 12 h after loading dose Continuous ECG, BP monitoring mandatory
Polysporin®	Apply to affected area BID/TID	Superficial infections	
Propofol	0.25-1 mg/kg IV	Procedural sedation, also refractory status epilepticus Rapid sequence intubation	Short acting Anesthetic/sedative (complication = apnea, decreased BP)
Salbutamol	2 puffs inhaled q4-6 h max 12 puffs/d	Asthma Reactive airways COPD	Caution with cardiac abnormalities
Thiamine	100 mg IV/IM initially, then 50-100 mg IM/IV/PO once daily x3 d	To treat/prevent Wernicke's encephalopathy	Caution use in pregnancy

Landmark Emergency Medicine Trials

Trial Name	Reference	Clinical Trial Details
DIVERTICULITIS		
DINAMO	Ann Surg. 2021;274:e435	**Title**: Efficacy and Safety of Nonantibiotic Outpatient Treatment in Mild Acute Diverticulitis **Purpose**: To support that uncomplicated acute diverticulitis can be treated using outpatient care without antibiotics. **Methods**: A Prospective, multicentre, open-label, RCT trial was conducted with 480 patients diagnosed with uncomplicated mild diverticulitis using CT. Patients were randomized to the classical treatment with antibiotics and without antibiotics. The outcome of interest was hospital admission. **Results**: 14/238 patients treated with antibiotics were admitted to hospital and 8/242 patients treated without antibiotics were admitted to hospital. **Conclusion**: The results show that treatment of uncomplicated mild diverticulitis can be effectively conducted as an outpatient without use of antibiotics.
CONCUSSION		
NCT03564210	JAMA Pediatr. 2021;175:1124-1131	**Title Title**: Effect of Screen Time on Recovery from Concussion **Purpose**: To determine if screen time during the first 48 h after injury has an impact on the duration of concussive symptoms. **Methods**: RCT consisting of 125 patients who were permitted to engage in unrestricted screen time or advised to abstain from screen time for 48 h after injury. The primary outcome of concern was days needed for resolution of concussive symptoms (<3 on post-concussive symptom scale). **Results**: The treatment group with unrestricted screen time had a significantly longer recovery time when compared to the group advised to abstain from screen time - 8 d and 3.5 d, respectively. **Conclusion**: The results of this study show that abstention from screen time during the first 48 h may reduce the duration of concussive symptoms.
SHOCK		
CLASSIC	NEJM 2022;386:2459-2470	Title: Restriction of Intravenous Fluid in ICU Patients with Septic Shock **Purpose**: To determine the effect of standard intravenous (IV) fluids or restricted IV fluids on mortality in patients with septic shock. **Methods**: RCT of 1554 patients with septic shock (≤12 h) who received at least 1L of IV fluid were assigned to either restricted IV fluid or standard IV fluid therapy. Primary outcome was death within 90 d. **Results**: Death resulted in 42.3% of the fluid-restricted group (median 1798 mL IV fluids), whereas death resulted in 42.1% of patients in the standard-fluid group (median 3811 mL IV fluids). Serious adverse events in restricted and standard-fluid groups occurred in 29.4% and 30.8% of patients, respectively. **Conclusion**: In patients with septic shock, IV fluid restriction does not result in fewer deaths within 90 d as compared to standard IV fluid therapy.
STROKE		
SELECT2	NEJM 2023;388:1259-1271	**Title**: Trial of Endovascular Thrombectomy for Large Ischemic Strokes **Purpose**: To evaluate efficacy and safety of endovascular thrombectomy in patients with large ischemic strokes (within 24 h of onset). **Methods**: A prospective Phase 3, randomized, open-label, international Phase 3 RCT involving patients assigned in a 1:1 ratio to endovascular thrombectomy plus medical care, or medical care alone. **Results**: Thrombectomy resulted in better functional outcomes using a Modified Rankin Scale (OR 1.51 [(95% CI, 1.20-1.89)]; P<0.001) than medical care but was associated with vascular complications. **Conclusion**: Endovascular thrombectomy improves functional outcomes in patients with large ischemic strokes but carries a risk of vascular complications.

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Endocrinology

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Acronyms

A1c	hemoglobin A1c
AAA	abdominal aortic aneurysm
Ab	antibodies
ABCA1	Adenosine triphosphate-binding cassette transporter A1
ACEI	angiotensin converting enzyme inhibitor
ACR	albumin-creatinine ratio
ADH	antidiuretic hormone
AG	anion gap
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ApoC2	apolipoprotein C2
ApoE4	apolipoprotein E4
ARB	angiotensin receptor blockers
ARR	absolute risk reduction
AVP	arginine vasopressin
BG	blood glucose
BMD	bone mineral density
BMI	body-mass index
CAH	congenital adrenal hyperplasia
CHO	carbohydrates
CK	creatine kinase
CKD	chronic kidney disease
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CVD	cardiovascular disease
DDAVP	desmopressin (1-deamino-8-D-arginine vasopressin)
DHEA	dehydroepiandrosterone
DI	diabetes insipidus
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DXM	dexamethasone
DVT	deep vein thrombosis
ECF	extracellular fluid
ECFV	extracellular fluid volume
FFA	free fatty acids
FNA	fine needle aspiration
FPG	fasting plasma glucose
GFR	glomerular filtration rate
GHRH	growth hormone releasing hormone
GLP-1	glucagon-like peptide 1
GnRH	gonadotropin releasing hormone
Hb	hemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HHS	hyperosmolar hyperglycemic state
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPA	hypothalamic pituitary adrenal
Hs-CRP	highly-sensitive C-reactive protein
HVA	homovanillic acid
ICF	intracellular fluid
IDL	intermediate density lipoprotein
IFG	impaired fasting glucose
IGF2	insulin-like growth factor 2
IGT	impaired glucose tolerance
JGA	juxtaglomerular apparatus
LCAT	lecithin-cholesterol acyltransferase
LDL	low density lipoprotein
LDL-C	low density lipoprotein-cholesterol
LDL-R	low density lipoprotein receptor
LP	lipoprotein
LP(a)	lipoprotein (a)
LPL	lipoprotein lipase
MEN	multiple endocrine neoplasia
MMI	methimazole
MTC	medullary thyroid cancer
NS	normal saline
OSA	obstructive sleep apnea
OGTT	oral glucose tolerance test
PA	primary aldosteronism
PAD	peripheral arterial disease
PCOS	polycystic ovary syndrome
PCSK9	proprotein convertase subtilisin/kexin type 9
POMC	pro-opiomelanocorticotropin
PRL	prolactin
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
PTU	propylthiouracil
RAAS	renin-angiotensin-aldosterone system
RAI	radioactive iodine
RAIU	radioactive iodine uptake
RANKL	receptor activator of nuclear factor-κB ligand
RH	releasing hormone
RRR	relative risk reduction
SA	secondary aldosteronism
SGLT2i	sodium-glucose cotransporter-2 inhibitor
SHBG	sex hormone-binding globulin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TBG	thyroid-binding globulin
TC	total cholesterol
TG	triglycerides
TgAb	thyroglobulin antibodies
TPOAb	anti-thyroid peroxidase antibodies
TRAb	Thyroid stimulating hormone receptor antibodies
TRH	thyrotropin-releasing hormone
TSI	thyroid stimulating immunoglobulin
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
WC	waist circumference

Basic Anatomy Review

Major Endocrine Organs

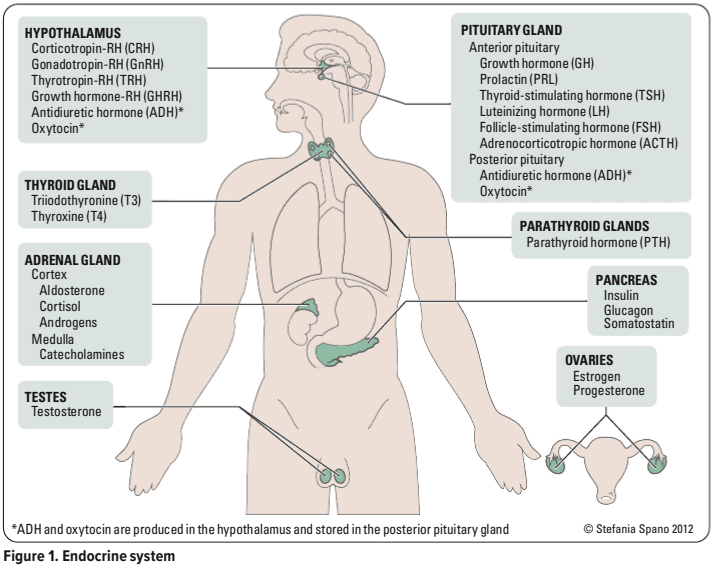


Figure 1. Endocrine system

Dyslipidemias

Definition

- metabolic disorders characterized by elevations of fasting plasma LDL-C, and/or TG, and/or low HDL-cholesterol

Overview of Lipid Transport

- lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apolipoproteins, and phospholipids
- lipoproteins transport lipids within the body
- apolipoproteins serve as enzyme cofactors, promote clearance of the particle by interacting with cellular receptors, and stabilize the lipoprotein micelle

Table 1. Lipoproteins

Lipoprotein	Function
Chylomicron	Transports dietary TG from gut to adipose tissue and muscle
VLDL	Transports hepatic synthesized TG from liver to adipose tissue and muscle
IDL	Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core Enriched in cholesterol esters
LDL	Cholesterol rich atherogenic particles Formed by further removal of residual TG from IDL core by hepatic lipase
HDL	Transports cholesterol from peripheral tissues to liver Acts as a reservoir for apolipoproteins

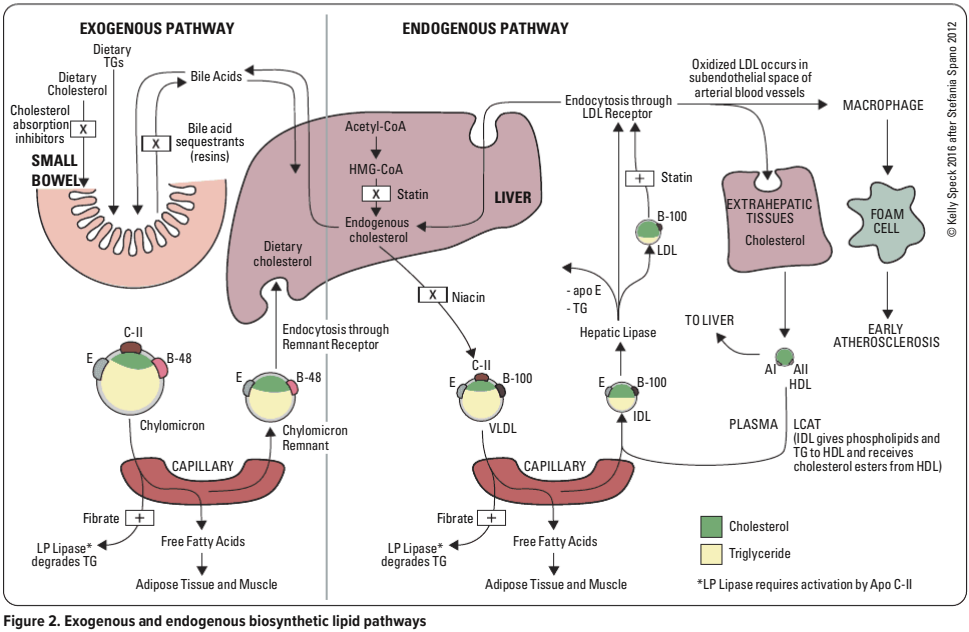


Figure 2. Exogenous and endogenous biosynthetic lipid pathways

Primary Dyslipidemias (rare)

Definition

- caused by a genetic defect(s) in lipid metabolism

Table 2. Primary Dyslipidemias

Condition	Main Lab Abnormality	Mechanism	Clinical Features	Treatment
Familial Hypercholesterolemia	↑ Total cholesterol ↑ LDL cholesterol	Genetic defect in LDLR (most common), PCSK9, or ApoB An autosomal dominant condition that can be homozygous or heterozygous Impacts liver's ability to clear LDL from the circulation	Tendinous xanthomatosis (achilles, patellar, and extensor tendons of hand) Arcus cornealis Xanthelasmata Heterozygotes: premature CAD, 50% risk of MI in men by age 30 Homozygotes: manifest CAD and other vascular disease early in childhood which can be fatal (in <20 y/o)	Maximally tolerated statin as initial drug therapy, addition of second drug (ezetimibe and/or PCSK9 inhibitor) as second line, third line for homozygotes is portacaval shunt or LDL apheresis; potential liver transplant Refer to lipid specialist in drug-resistant hypercholesterolemia
Familial Combined Hyperlipidemia	↑ ApoB ↑ TGs ↑ LDL	Increased production of ApoB-100-containing lipoproteins from the liver	Premature coronary heart disease, xanthelasma, and obesity	Statins as initial drug therapy Addition of ezetimibe and/or PCSK9 inhibitor if LDL lowering is not achieved. May consider fibrate if elevated TG
Polygenic Familial Hypercholesterolemia	↑ LDL	Mild defects in multiple genes responsible for LDL metabolism: LDL-R, ApoB, ApoE4	Higher risk of cardiovascular disease similar to familial hypercholesterolemia for patients older than 40	Statins as first line Use ezetimibe, bile acid sequestrants, PCSK9 inhibitor, or nicotinic acid as alternatives (if not tolerated) or in addition
Hereditary Chylomicronemia **Familial lipoprotein lipase deficiency** (e.g. Familial Hypertriglyceridemia/type IV familial dyslipidemia) **ApoC2 deficiency**	↑ TG from excess chylomicron particles	Lipoprotein lipase deficiency: prevents proper digestion and storage of fats leading to massive accumulation of triglyceride rich chylomicron particles $ApoC_2$ deficiency: prevents activation of lipoprotein lipase leading to massive accumulation of triglyceride rich chylomicron particles	Presents at infancy (LPL), adolescence to adulthood ($ApoC_2$) Abdominal complaints (pain, hepatosplenomegaly, pancreatitis) Lipemia retinalis Eruptive xanthomata	<10-15% of calories from fat Supplement with essential fatty acids, fat-soluble vitamins Plasmapheresis may help individuals with $ApoC_2$ mutation
Familial Hypoalphalipoproteinemia	↓ HDL cholesterol	Autosomal dominant inheritance of a mutation in the ABCA1 or the $ApoA_1$ gene	Premature atherosclerosis Cerebrovascular disease	Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present
Tangier Disease	↓ HDL cholesterol	Autosomal recessive inheritance of mutations in the ABCA1 gene Impaired HDL-mediated cholesterol efflux from macrophages and impaired intracellular lipid trafficking	Mild hypertriglyceridemia Neuropathy Enlarged, orange-coloured tonsils Premature atherosclerosis Splenomegaly Hepatomegaly Corneal clouding T2DM	Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present

Secondary Dyslipidemias

Definition
- caused by acquired medical conditions or lifestyle factors that affect lipid metabolism

Table 3. Etiology of Secondary Dyslipidemias

Hypercholesterolemia	Low HDL	Hypertriglyceridemia
Endocrine: hypothyroidism (small dense LDL with T2DM and obesity, with normal LDL level)	**Endocrine:** obesity/metabolic syndrome, DM	**Endocrine:** obesity/metabolic syndrome, DM
Renal: nephrotic syndrome, CKD	**Drugs:** β-blockers, anabolic steroids	**Renal:** nephrotic syndrome, CKD
Immunologic: monoclonal gammopathy	**Other:** acute infections, inflammatory conditions	**Drugs:** corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
Hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)		**Lifestyle:** alcohol, high carbohydrate/high fat diet
Nutritional: anorexia nervosa		**Other:** pregnancy
Drugs: cyclosporin, carbamazepine, steroids		
Lifestyle: smoking, obesity		

Dyslipidemia and the Risk for Coronary Artery Disease

- increased LDL is a major risk factor for atherosclerosis and CAD
- increased HDL is associated with decreased CVD and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3-9 mmol/L) is an independent risk factor for CAD, especially in people with DM and in post-menopausal women

Screening
- screen men and women ≥40 yr or post-menopausal women
- if the following risk factors are present, screen at any age:
  - DM
  - current cigarette smoking or COPD
  - HTN (sBP >140, dBP >90), hypertensive diseases of pregnancy
  - obesity (BMI ≥30 kg/m^2)
  - family history of premature CVD or dyslipidemia

Familial Hypercholesterolemia and Cardiovascular Risk Calculators

Risk calculators such as Framingham and SCORE do not apply to patients with familial hypercholesterolemia

Consider all adults with familial hypercholesterolemia as "high-risk"

Treatment Effect
- Each 1.0 mmol/L decrease in LDL corresponds to approximately 20-25% relative risk reduction in cardiovascular disease
- Statins lower LDL by about 30-40%
- Ezetimibe lowers LDL by about 18%
- PCSK9 inhibitors lowers LDL by about 50%

6% Rule

If the dose of a statin is doubled, there is approximately a 6% increase in the LDL lowering efficacy

- clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
- clinical or radiological evidence of AAA
- clinical evidence of atherosclerosis
- inflammatory disease (rheumatoid arthritis, SLE, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease)
- HIV infection on highly active antiretroviral therapy (HAART)
- CKD (estimated GFR <60 mL/min/1.73 m^2)
- erectile dysfunction
- high-risk ethnicity: South Asian, Indigenous peoples

• screen children with a family history of hypercholesterolemia or chylomicronemia
• components of screening:
  - history and physical examination, lipid panel (total cholesterol, LDL-C, HDL-cholesterol, TG), non-HDL cholesterol, BG, eGFR
  - optional: urine ACR, ApoB
• ApoB
  - each atherogenic particle (VLDL, IDL, LDL, and lipoprotein A) contains one molecule of ApoB
  - serum (ApoB) reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high-risk patients and those with metabolic syndrome
• LP(a) levels may help stratify those at intermediate risk, but is not recommended for routine measurement (only measured once in a patient's lifetime)
• coronary artery calcium (CAC) may help stratify those at intermediate risk
• CRP levels
  - highly sensitive acute phase reactant (non-specific)
  - may be clinically useful to identify those at a higher risk of CVD than predicted by the global risk assessment

CVD Risk Assessment

• Framingham Risk Score (FRS): 10 yr risk of major CVD event. Calculated based on gender, age, total cholesterol, HDL-cholesterol, sBP, and smoking (≥20%: high-risk; 10-19.9%: moderate risk; <10%: low-risk)
• Reynolds Risk Score: 10 yr risk of major CVD event. Calculated based on age, sBP, total cholesterol, HDL-cholesterol, high sensitivity CRP, family history of MI

For Statin Follow-Up

- Liver enzymes and lipid profile: liver enzymes measured at the beginning of treatment, then once after therapy initiated. Lipids (once stabilized) measured annually. Order both if patient complains of jaundice, right upper quadrant pain, dark urine
- CK at baseline and if patient complains of myalgia
- Discontinue statin if CK >10x upper limit of normal or patient has persistent myalgia

See Landmark Endocrinology Trials for more information on the JUPITER trial. It details the effects of statin treatment on cardiovascular events in patients with elevated high-sensitivity CRP levels.

Treatment of Dyslipidemias

Approach to Treatment

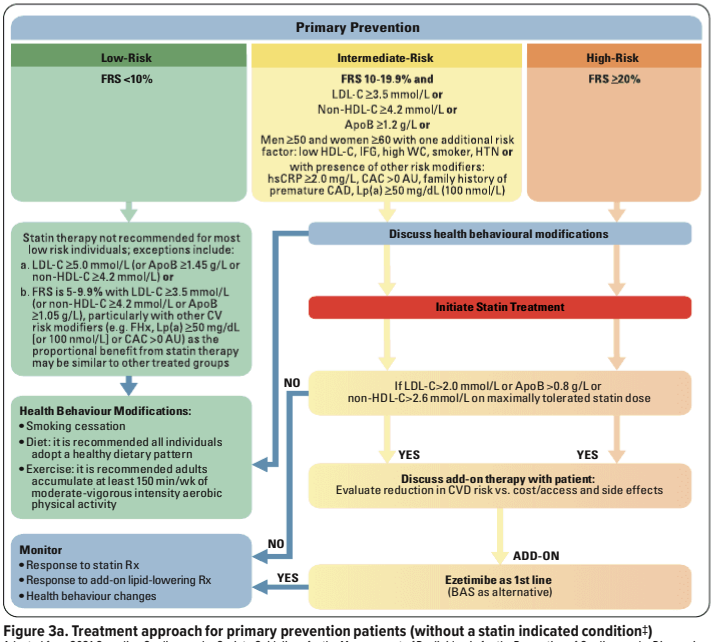

Primary Prevention
Low-Risk
FRS <10%
Intermediate-Risk
FRS 10-19.9% and
LDL-C ≥3.5 mmol/L or
Non-HDL-C ≥4.2 mmol/L or
ApoB ≥1.2 g/L or
Men ≥50 and women ≥60 with one additional risk factor: low HDL-C, IFG, high WC, smoker, HTN or
with presence of other risk modifiers: hsCRP ≥2.0 mg/L, CAC >0 AU, family history of premature CAD, Lp(a) ≥50 mg/dL (100 nmol/L)
High-Risk
FRS ≥20%
Statin therapy not recommended for most low risk individuals; exceptions include:
a. LDL-C ≥5.0 mmol/L (or ApoB ≥1.45 g/L or non-HDL-C ≥4.2 mmol/L) or
b. FRS is 5-9.9% with LDL-C ≥3.5 mmol/L (or non-HDL-C ≥4.2 mmol/L or ApoB ≥1.05 g/L), particularly with other CV risk modifiers (e.g. FHx, Lp(a) ≥50 mg/dL (or 100 nmol/L) or CAC >0 AU) as the proportional benefit from statin therapy may be similar to other treated groups
Discuss health behavioural modifications
Initiate Statin Treatment
Health Behaviour Modifications:
• Smoking cessation
• Diet: it is recommended all individuals adopt a healthy dietary pattern
• Exercise: it is recommended adults accumulate at least 150 min/wk of moderate-vigorous intensity aerobic physical activity
NO
If LDL-C>2.0 mmol/L or ApoB >0.8 g/L or non-HDL-C>2.6 mmol/L on maximally tolerated statin dose
YES
YES
Discuss add-on therapy with patient:
Evaluate reduction in CVD risk vs. cost/access and side effects
Monitor
• Response to statin Rx
• Response to add-on lipid-lowering Rx
• Health behaviour changes
NO
YES
ADD-ON
Ezetimibe as 1st line
(BAS as alternative)

Figure 3a. Treatment approach for primary prevention patients (without a statin indicated condition‡)
Adapted from 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Cardiovascular Society.

2021 Canadian Cardiovascular Society Guidelines on the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult
Can J Cardiol 2021; S0828-282X(21)00165-3

- Patients with clinical atherosclerosis, AAA, LDL-C ≥5.0 mmol/L, and most with diabetes or CKD should be started on statin therapy.
- Icosapent ethyl should be used to decrease the risk of CV events in people with ASCVD or with diabetes and >1 CVD risk factor who have TG 1.5-5.6 mmol/L even if on maximally tolerated statin.
- Lipid/lipoprotein screening is recommended in patients >40 yr or at any age for those at increased risk.
- Non-HDL cholesterol or ApoB are preferred to LDL-C as lipid parameters for screening in patients with TG >1.5 mmol/L.
- LP(a) should be measured once in a person's lifetime as part of initial lipid screening to assess cardiovascular risk.
- Lipid-lowering therapy should be intensified with ezetimibe and/or PCSK9 inhibitors in patients with LDL-C remaining ≥1.8 mmol/L (or non-HDL cholesterol ≥2.4 mmol/L or ApoB ≥0.7 g/L) on a maximally tolerated statin dose.

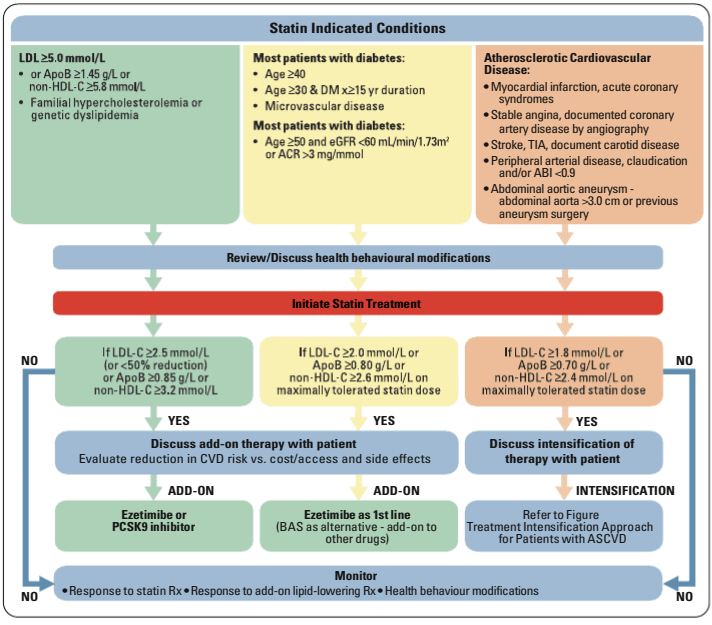

Statin Indicated Conditions
LDL ≥5.0 mmol/L
• or ApoB ≥1.45 g/L or non-HDL-C ≥5.8 mmol/L
• Familial hypercholesterolemia or genetic dyslipidemia
Most patients with diabetes:
• Age ≥40
• Age ≥30 & DM x≥15 yr duration
• Microvascular disease
Most patients with diabetes:
• Age ≥50 and eGFR <60 mL/min/1.73m² or ACR >3 mg/mmol
Atherosclerotic Cardiovascular Disease:
• Myocardial infarction, acute coronary syndromes
• Stable angina, documented coronary artery disease by angiography
• Stroke, TIA, document carotid disease
• Peripheral arterial disease, claudication and/or ABI <0.9
• Abdominal aortic aneurysm - abdominal aorta >3.0 cm or previous aneurysm surgery
Review/Discuss health behavioural modifications
Initiate Statin Treatment
NO
If LDL-C ≥2.5 mmol/L (or <50% reduction) or ApoB ≥0.85 g/L or non-HDL-C ≥3.2 mmol/L
If LDL-C ≥2.0 mmol/L or ApoB ≥0.80 g/L or non-HDL-C ≥2.6 mmol/L on maximally tolerated statin dose
If LDL-C ≥1.8 mmol/L or ApoB ≥0.70 g/L or non-HDL-C ≥2.4 mmol/L on maximally tolerated statin dose
NO
YES
YES
YES
Discuss add-on therapy with patient
Evaluate reduction in CVD risk vs. cost/access and side effects
Discuss intensification of therapy with patient
ADD-ON
ADD-ON
INTENSIFICATION
Ezetimibe or PCSK9 inhibitor
Ezetimibe as 1st line (BAS as alternative - add-on to other drugs)
Refer to Figure Treatment Intensification Approach for Patients with ASCVD
Monitor
• Response to statin Rx • Response to add-on lipid-lowering Rx • Health behaviour modifications
NO
NO

Figure 3b. Treatment approach for patients with a statin indicated condition

Adapted from 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Cardiovascular Society.

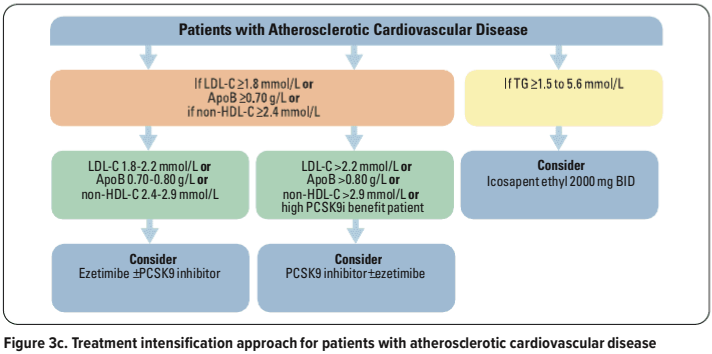

Patients with Atherosclerotic Cardiovascular Disease
If LDL-C ≥1.8 mmol/L or ApoB ≥0.70 g/L or if non-HDL-C ≥2.4 mmol/L
If TG ≥1.5 to 5.6 mmol/L
LDL-C 1.8-2.2 mmol/L or ApoB 0.70-0.80 g/L or non-HDL-C 2.4-2.9 mmol/L
LDL-C >2.2 mmol/L or ApoB >0.80 g/L or non-HDL-C >2.9 mmol/L or high PCSK9i benefit patient
Consider Icosapent ethyl 2000 mg BID
Consider Ezetimibe ±PCSK9 inhibitor
Consider PCSK9 inhibitor±ezetimibe

Figure 3c. Treatment intensification approach for patients with atherosclerotic cardiovascular disease (ASCVD)

Adapted from 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Cardiovascular Society.

See Landmark Endocrinology Trials table for more information on the REDUCE-IT trial. This study investigates the use of icosapent ethyl to reduce cardiovascular events.

Effects of Icosapent Ethyl and a Mineral Oil Comparator on Biomarkers - A REDUCE-IT Substudy
Circulation 2022; 146(5):372-9

Purpose: To investigate if treatment assignment in the REDUCE-IT trial influenced various biomarkers related to the risk of atherosclerosis.

Methods: Serum levels of interleukin-1β, interleukin-6, hs-CRP, oxidized LDL, homocysteine, LP(a), and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels were measured at baseline, 12 mo, 24 mo, and end-of-study visit.

Results : Treatment with icosapent ethyl had minimal effect on LP(a), homocysteine, oxidized LDL, interleukin-6, Lp-PLA2 activity, interleukin-1β, hs-CRP, or LDL cholesterol levels at 12 mo. Conversely, patients treated with mineral oil comparator showed increases in these biomarkers.

Conclusions : In the REDUCE-IT study, treatment with icosapent ethyl had minimal impact on several biomarkers linked to atherosclerotic disease, while levels increased in participants treated with mineral oil. Implications of these findings on the interpretation of overall risk reductions in clinical events observed in REDUCE-IT are uncertain.

Disorders of Glucose Metabolism

Overview of Glucose Regulation

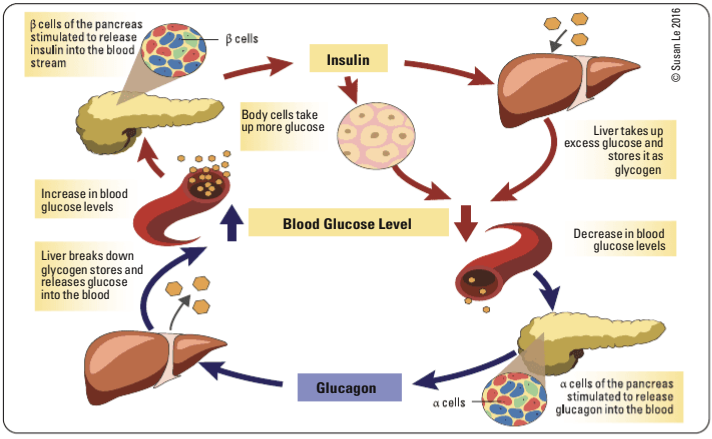

β cells of the pancreas stimulated to release insulin into the blood stream
β cells
Insulin
Body cells take up more glucose
Liver takes up excess glucose and stores it as glycogen
Increase in blood glucose levels
Blood Glucose Level
Decrease in blood glucose levels
Liver breaks down glycogen stores and releases glucose into the blood
Glucagon
α cells
α cells of the pancreas stimulated to release glucagon into the blood
© Susan Le 2016

Figure 4. Blood glucose regulation

Pre-Diabetes (Impaired Glucose Tolerance/Impaired Fasting Glucose)

- 1-5% per yr go on to develop DM
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance (5-10% of body weight)
- increased risk of developing macrovascular complications
- lifestyle modifications decrease progression to DM by 58%
- metformin decreases progression to DM by 31%

Diagnostic Criteria (Diabetes Canada 2018 Guidelines) (any of the following)

- IFG: FPG 6.1-6.9 mmol/L
- IGT: 2 h 75 g OGTT 7.8-11.0 mmol/L
- A1c: 6.0-6.4%

Diabetes Mellitus

Definition

- DM is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia
- chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys, and nerves, as well as an increased risk for macrovascular complications such as CVD, stroke, and peripheral vascular disease. Diabetes also increases the risk of heart failure

Diagnostic Criteria (as per Diabetes Canada 2018 Clinical Practice Guidelines)

- any one of the following is diagnostic:

Table 4. Diagnosis of Diabetes

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 h
or
A1c ≥6.5% (in adults)
Not for diagnosis of suspected T1DM, children, adolescents, or pregnant women
or
2hPG in a 75 g OGTT ≥11.1 mmol/L
or
Random PG ≥11.1 mmol/L
Random = any time of the day, without regard to the interval since last meal

- in the presence of hyperglycemia symptoms (polyuria, polydipsia, polyphagia, weight loss, blurry vision), a confirmatory test is not required
- in the absence of hyperglycemia symptoms, a repeat confirmatory test (FPG, A1c, 2hPG in a 75 g OGTT) on another day is required for diagnosis of diabetes

See Landmark Endocrinology Trials table for more information on the 4T trial. It details the efficacy of complex insulin regimen for patients with T2DM.

See Landmark Endocrinology Trials table for more information on the UKPDS trial. It compares the safety and efficacy of intensive blood-glucose control with sulphonylurea or insulin vs. conventional treatment on the risk of complications in T2DM.

See Landmark Endocrinology Trials table for more information on the DCCT trial. It details the use of intensive insulin injection therapy for the treatment of T1DM in patients with no cardiovascular history or severe diabetic complications.

Etiology and Pathophysiology

Table 5. Etiologic Classification of Diabetes Mellitus

I. T1DM immune-mediated or idiopathic β cell destruction, usually leading to absolute insulin deficiency (includes latent autoimmune diabetes in adults (LADA))

II. T2DM occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced

III. Other Specific Causes of DM

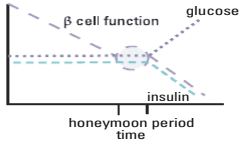
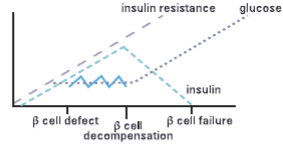
a. Genetic defects of β cell function (e.g. Maturity-Onset Diabetes of the Young (MODY; also known as monogenic diabetes)) or insulin action
b. Diseases of the exocrine pancreas:
Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis ("bronze diabetes")
c. Endocrinopathies:
Acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism
d. Drug-induced:
Glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, antipsychotics
e. Infections:
Congenital rubella, CMV, coxsackie
f. Genetic syndromes associated with DM:
Down's syndrome, Klinefelter's syndrome, Turner's syndrome

IV. Gestational Diabetes Mellitus (see Obstetrics, OB28)

Diabetes Canada 2018 Clinical Practice Guidelines

	Target
A1c	<7.0% (most adults)
Fasting plasma glucose	4-7 mmol/L
2h post-prandial glucose	5-10 mmol/L 5-8 mmol/L if not meeting target A1c and can be safely achieved
Lipids	LDL <2.0 or 50%
Blood pressure	<130/80

Table 6. Comparison of Type 1 and Type 2 Diabetes Mellitus

	Type 1	Type 2
Onset	Usually <30 yr of age	Usually >40 yr of age Increasing incidence in pediatric population 2° to obesity
Epidemiology	Traditionally more common in European populations Less common in Asian, Hispanic, Indigenous, and Black populations Accounts for 5-10% of all DM	More common in Black, Hispanic, Indigenous, and Asian populations Accounts for >90% of all DM
Etiology	Autoimmune or idiopathic	Complex and multifactorial
Genetics	Monozygotic twin concordance is 30-40% Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of T1DM Certain DQ alleles also confer a risk	Greater heritability than T1DM Monozygotic twin concordance is 70-90% Polygenic Non-HLA associated
Pathophysiology	Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion Autoimmune process is believed to be triggered by environmental factors (e.g. viruses, bovine milk protein, urea compounds) Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction 80% of β cell mass is destroyed before features of DM present	Impairment of insulin secretion, excess glucose production by the liver, insulin resistance in fat and muscle, impaired renal handling of glucose (SGLT2i), impaired incretin activity (decreased insulin production, excess glucagon production, enhanced carbohydrate absorption in the gut and increased appetite from the hypothalamus)
Natural History		
	After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin Once these cells are destroyed, there is complete insulin deficiency	Early on, glucose tolerance remains normal despite insulin resistance as β cells compensate with increased insulin production As insulin resistance and compensatory hyperinsulinemia continue, the β cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and DM
Circulating Autoantibodies	Islet cell Ab present in up to 60-85% Most common islet cell Ab is against glutamic acid decarboxylase (GAD) Up to 60% have Ab against insulin	<10%
Risk Factors	Personal history of other autoimmune diseases including Graves' disease, myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia Family history of autoimmune diseases	Age >40 yr Schizophrenia Abdominal obesity/overweight Fatty liver First-degree relative with DM Hyperuricemia Race/ethnicity (Black, Indigenous, Hispanic, Asian-American, Pacific Islander) Hx of IGT or IFG HTN Dyslipidemia Medications e.g. 2nd generation antipsychotics PCOS Hx of gestational DM or macrosomic baby (>9 lb or >4 kg)
Body Habitus	Normal to thin	Typically overweight with increased central obesity
Treatment	Insulin	Lifestyle modification Non-insulin antihyperglycemic agents - unless contraindicated, metformin should be the initial antihyperglycemic agent of choice. Additional agents to be selected on the basis of clinically relevant issues, such as CV risk, eGFR, glucose-lowering effectiveness, risk of hypoglycemia, and effect on body weight Insulin therapy
Acute Complications	DKA	HHS DKA
Screening	Subclinical prodrome can be detected in first and second-degree relatives of those with T1DM by the presence of pancreatic islet autoantibodies	Screen individuals with risk factors

Treatment of Diabetes

Glycemic Targets

- A1c reflects glycemic control over 3 mo and is a measure of long-term glycemic control
- A1c is recommended to be measured once every 3-6 mo and personalized A1c targets should be set for patients based on their frailty or functional dependence and life expectancy
- therapy for most individuals living with T1DM or T2DM (especially younger patients) should be targeted to achieve an A1c ≤7.0% in order to reduce the risk of microvascular and, if implemented early in the course of disease, macrovascular complications
- more intensive glucose control, A1c <6.5%, may be targeted to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia
- less stringent A1c targets (7.1-8.5%) may be more appropriate in patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to achieve an A1c <7.0% despite intensified basal and bolus insulin therapy
- there may be harm associated with strategy to target A1c <6.0% (see *ACCORD Trial, E62*)
- A1c can be slightly increased in iron deficiency, vitamin B_{12} deficiency, alcoholism, and CKD, independent of glycemic status
- A1c can be slightly decreased in chronic liver disease, reticulocytosis, ingestion of ASA, vitamin C or E, and splenomegaly, independent of glycemic status
- timing and frequency of self-monitored blood glucose is determined by the type of diabetes, treatment, and the individual's capacity to use the information
- most people with type 1 or type 2 diabetes should aim for time in range (glucose 3.9-10 mmol/l) >70%, time above range <25% and time below range <4%
- continuous glucose monitoring devices may be suggested for some people living with diabetes to optimize their diabetes self-management

Diet

- nutritional therapy can reduce A1c by 1-2%
- it is recommended to intake 45-60% carbohydrates, 15-20% protein, and <35% fats as a percentage of total daily energy
- it is recommended to intake <7% of saturated fats and <10% of polyunsaturated fats as a percentage of total daily calories
- it is recommended to replace high-glycemic-index carbohydrates with low-glycemic-index carbohydrates and increase fibre intake
- limit sodium, alcohol, and caffeine intake
- people with diabetes should adopt dietary patterns that result in the greatest adherence based on their values and preferences
- type 1: carbohydrate counting is used to titrate prandial insulin dose
- type 2: weight reduction to help control blood glucose levels

Lifestyle

- losing 5-10% of the initial body weight can improve insulin sensitivity, glycemic control, hypertension, and dyslipidemia in people with T2DM
- regular physical exercise can improve insulin sensitivity, lower lipid concentrations, and control blood pressure. At least 150 min per wk of moderate-vigorous aerobic exercise and at least 2 sessions per wk of resistance exercise are recommended
- smoking cessation, referral to diabetes education clinic, psychosocial support

Medical Treatment: Non-Insulin Antihyperglycemic Agents (T2DM)

- initiate non-insulin antihyperglycemic therapy (generally metformin first line) within 3 mo if lifestyle management does not result in adequate glycemic control
- if the initial A1c value is more than 1.5% higher than the patient's personalized A1c target, initiate pharmacologic therapy with metformin immediately, and consider insulin or a combination of therapies
- if presenting in metabolic decompensation, begin with insulin therapy immediately
- adjust dose or add additional pharmacologic therapy in a timely fashion to achieve target A1c within 3-6 mo of diagnosis
- see *Common Medications, E57* for details on antihyperglycemic agents

Medical Treatment: Insulin

- used for T1DM at onset, may be used in T2DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- basal insulin: to control blood sugar (produced by liver) during periods of fasting; slow onset of action, long-acting
- bolus insulin: required to dispose of glucose from a meal or BG correction; rapid onset of action, short-acting
- estimated total daily insulin requirement: often start with 0.3-0.5 units/kg/d (see *Table 7, E12*)

Who should receive statins (regardless of LDL-C level)

- Clinical CVD
- Age >40 yr
- Microvascular complications or
- Diabetes >15 yr duration and age >30 yr
- Warrants therapy based on the 2016 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia

Who should receive ACEI/ARB (regardless of baseline BP)

- Clinical CVD
- Age >55 years with an additional CV risk factor or end organ damage (albuminuria, retinopathy, left ventricular hypertrophy)
- Microvascular complications

ABCDES of Diabetes Care

A1c targets (<7.0%)
Blood pressure (<130/80)
Cholesterol (LDL-C <2.0 mmol/L)
Drugs for CVD risk reduction
Exercise goals and healthy eating
Smoking cessation
Screening for complications
Stress management

Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care
NEJM 2018;379:547-556
Purpose: To determine if a closed-loop delivery system (artificial pancreas) can improve glycemic control in patients with T2DM receiving noncritical care.
Methods: Patients (n=136) received either closed-loop insulin delivery or conventional subcutaneous insulin therapy. The percentage of time the sensor glucose measurement was within 5.6 to 10.0 mmol/L was measured.
Results: Closed-loop insulin delivery was more effective at maintaining glucose within the target range (95% CI: 18.6-30.0; P<0.001). Patients on closed-loop insulin therapy had lower mean glucose levels (P<0.001). There was no difference in duration of hypoglycemia or amount of insulin delivered between groups.
Conclusions: The use of an automated, closed-loop insulin-delivery system (artificial pancreas) resulted in significantly better glycemic control among inpatients with T2DM receiving non-critical care.

Closed-loop insulin delivery using an artificial pancreas has also shown promise in patients with T1DM (NEJM 2019;381:1707-17).

See Landmark Endocrinology Trials table for more information on the ACCORD trial. It details the effects of intensive glucose control in patients with T2DM and cardiovascular risk factors.

See Landmark Endocrinology Trials table for more information on the ACCORD Trial – Blood Pressure Control. It details the effects of intensive blood pressure control for patients with T2DM.

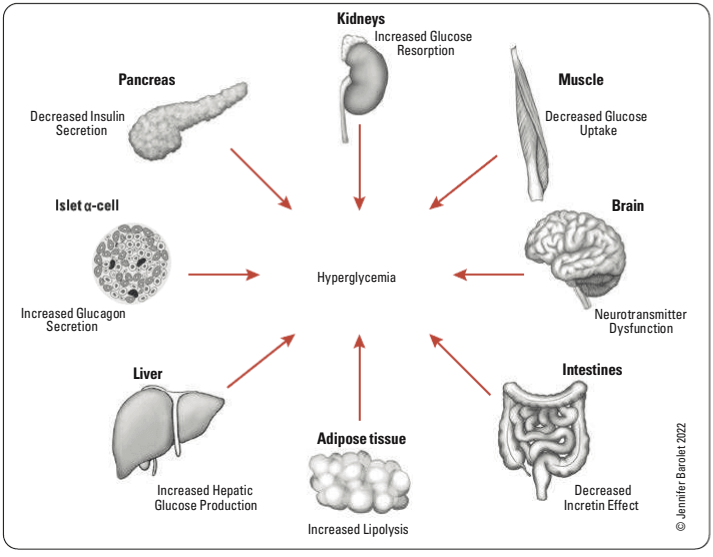
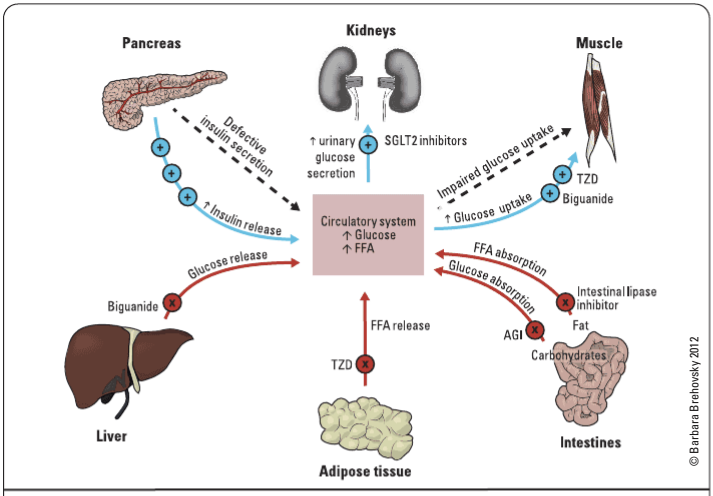


Figure 5. Ominous octet: factors leading to hyperglycemia

See Landmark Endocrinology Trials table for more information on the ACCORD Trial – Combination Lipid Therapy. It details the effects of combinational lipid therapy for patients with T2DM.

See Landmark Endocrinology Trials table for more information on the PREDIMED trial. It details the effects of a Mediterranean diet on reducing major cardiovascular events in patients with T2DM or other high cardiovascular risk factors.



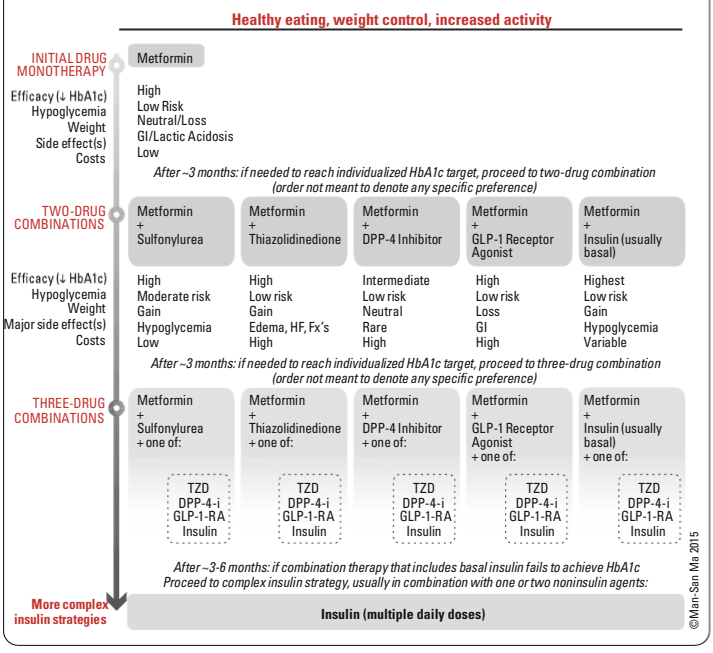


Figure 6. Management of hyperglycemia in T2DM

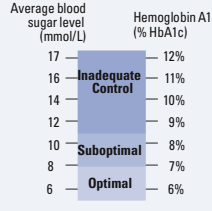
Adapted from Canadian Journal of Diabetes, Volume 42, Lipscombe L, Booth Gillian, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, Page S92, Copyright (2020), with permission from Elsevier

Sick Day Management

If patient is ill and is unable to maintain adequate fluid intake, or has an acute decline in renal function, they should hold the following medications:

SAD MANS
Sulfonylureas
ACEIs
Diuretics and direct renin inhibitors
Metformin
ARBs
NSAIDs
SGLT2i

Conversion Chart for Percentage HbA1c to Average Blood Sugar Control



Conversion chart adapted from Nathan DM, et al. The clinical information value of a glycosylated hemoglobin assay. NEJM 1984;310:341-346

The 8 I's Precipitating DKA
Infection
Ischemia or Infarction
Iatrogenic (glucocorticoids)
Intoxication
Insulin missed
Initial presentation
Intra-abdominal process (e.g. pancreatitis, cholecystitis)
Intraoperative/perioperative stress

Table 7. Available Insulin Formulations

Insulin Type (trade name)	Onset	Peak	Duration
PRANDIAL (BOLUS) INSULINS			
Rapid-acting insulin analogues			
Insulin aspart (NovoRapid®)	10-15 min	1-1.5 h	3-5 h
Insulin faster aspart (Fiasp®)	4 min	1 h	3-4 h
Insulin lispro (Humalog®, Humalog 200 units/mL)	10-15 min	1-2 h	3.5-4.75 h
Insulin glulisine (Apidra®)	10-15 min	1-1.5 h	3-5 h
Short-acting insulins	30 min	2-3 h	6.5 h
Humulin R®			
Novolin Toronto®			
BASAL INSULINS			
Intermediate-acting	1-3 h	5-8 h	Up to 18 h
Humulin N®			
Novolin NPH®			
Long-acting basal insulin analogues			
Insulin detemir (Levemir®)	90 min	Not applicable	Up to 24 h (detemir 16-24 h)
Insulin glargine 100 units/mL (Lantus®/Basaglar®)	90 min		Up to 24 h (glargine 24 h)
Insulin glargine 300 units/mL (Toujeo®)	Up to 6 h		Up to 30 h
Insulin glargine (Basaglar®)	90 min		Up to 24 h (glargine 24 h)
Insulin degludec (Tresiba®)	60 min		Ultralong acting (42 h)
PRE-MIXED INSULINS			
Premixed regular insulin – NPH	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Humulin 30/70®			
Novolin 30/70®			
Premixed insulin analogues			
Biphasic insulin aspart (NovoMix 30®)			
Insulin lispro/lispro protamine (Humulin 30/70, Novolin 30/70, Novomix 30 and Humalog Mix 25)			

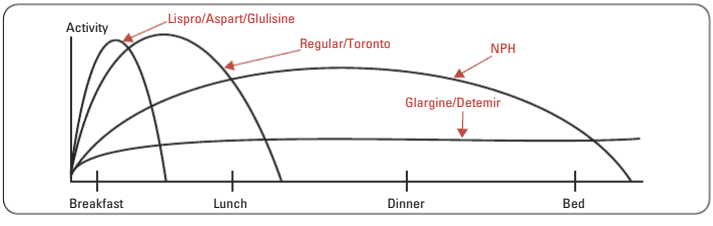


Figure 7. Duration of activity of different insulins

Table 8. Insulin Regimens for T2DM and T1DM

	Regimen	Administration
T1DM	Basal-bolus (multiple daily injections (MDI))	Estimated total insulin requirement is 0.5-0.7 U/kg 40% is given as basal insulin at bedtime 20% is given as bolus insulin before breakfast, lunch, and dinner
	Premixed	Estimated total insulin requirement is 0.5-0.7 U/kg 2/3 dose is given as pre-mixed insulin before breakfast 1/3 dose is given as pre-mixed insulin before dinner
T2DM	Non-insulin antihyperglycemic agent + basal insulin	Titrate up by 1 unit until FPG <7.0 mmol/L

*Bolus insulin: Aspart, Glulisine, Lispro; *Basal insulin: Glargine, Detemir, NPH; *Pre-mixed insulin: Humulin 30/70, Novolin 30/70, Novomix 30, and Humalog Mix2

Table 9. Titrating Insulin Doses

Hyperglycemic Reading	Insulin Correction
High AM sugar	Increase bedtime basal insulin
High lunch sugar	Increase AM rapid/regular insulin
High supper sugar	Increase lunch rapid/regular insulin or increase AM basal insulin
High bedtime sugar	Increase supper rapid/regular insulin

Insulin Dose Schedules

Table 10. Insulin Titration and Titration Suggestions for T2DM (as per Diabetes Canada 2018 Clinical Practice Guidelines)

Basal Insulin Only – Add-on to Anti-hyperglycemic Agents	
See above summary for A1c, BG targets Most patients will need 40-50 units/d to achieve target but there is no maximum dose Start at a low dose of 10 U at bedtime (lower for lean patients <50 kg) Titrate dose accordingly until fasting BG target is achieved (see CDA guidelines for appropriate titration) If fasting hypoglycemia, dose of bedtime basal should be reduced If daytime hypoglycemia, reduce dose of oral antihyperglycemic agents (especially secretagogues)	Dosing and Titration Example Starting dose – 10 U at bedtime Increase dose by 1 U every 1 night until fasting BG has reached target of 4-7 mmol/L
Basal-Bolus Insulins	
When addition of basal insulin to anti-hyperglycemic agents is insufficient to reach target BG, bolus (prandial) insulin should be added before meals Option exists to only add bolus insulin to the meal with the highest postprandial BG as a starting point Insulin secretagogues typically stopped when bolus (prandial) insulin added; metformin is continued Maintain the basal dose and add bolus insulin with each meal at a dose equivalent to 10% of basal dose Total Daily Insulin (TDI) = 0.3-0.5 U/kg; 40% TDI = basal, 20% TDI = prandial (bolus) prior to each meal Adjust basal insulin to achieve target fasting BG, bolus insulin to achieve postprandial BG levels (5-10 mmol/L), or preprandial BG levels for subsequent meal (4-7 mmol/L)	Dosing and Titration Example TDI = 0.5 U/kg: 0.5 x 100 kg = 50 U Basal insulin = 40% of TDI 40% x 50 U = 20 U; basal bedtime = 20 U Bolus insulin = 60% of TDI 60% x 50 U = 30 U; 10 U dosed with each meal
Premixed Insulin Before Breakfast and Before Dinner	
Target fasting and pre-dinner BG levels of 4-7 mmol/L Most patients with T2DM need 40-50 U BID to achieve target, but no maximum dose Start at a low dose of 5-10 U BID (before breakfast and before dinner) Patients can self-titrate by increasing insulin dose by 1 U/d until pre-dinner (breakfast dose) or fasting BG (dinner dose) at target Continue metformin and consider stopping secretagogue	Dosing and Titration Example 10 U before breakfast, 10 U before dinner Increase breakfast dose by 1 U/d until pre-dinner BG has reached target Increase dinner dose by 1 U/d until fasting BG has reached target

- Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD) = change in blood glucose per unit of insulin
  - BG <4 mmol/L: call physician and give 15 g of rapid-acting carbohydrates and recheck in 15 min
  - BG between 4 to 8: no additional insulin
  - BG between 8 to (8 + CF): give one additional unit
  - BG between (8 + CF) to (8 + 2CF): give two additional units
  - BG between (8 + 2CF) to (8 + 3CF): give three additional units

Insulin Pump Therapy: Continuous Subcutaneous Insulin Infusion (CSII)

- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine, or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus based on carbohydrate:insulin ratios
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected or pump malfunctions
- coverage for insulin pumps for individuals with T1DM varies by province

Acute Complications

Table 11. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

	Diabetic Ketoacidosis (DKA)	Hyperosmolar Hyperglycemic State (HHS)
Pathophysiology	Usually occurs in T1DM Insulin deficiency with ↑ counterregulatory hormones (glucagon, cortisol, catecholamines, GH) Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise) Unopposed hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na^+ (water shift to ECF causing pseudohyponatremia) Fat mobilization → ↑ FFA → ketoacids → metabolic acidosis Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria Total body K^+ depletion but serum K^+ may be normal or elevated, 2° to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality	Occurs in T2DM Often precipitated by sepsis, stroke, MI, CHF, renal failure, trauma, drugs (glucocorticoids, immunosuppressants, phenytoin, diuretics), dialysis, recent surgery, burns Partial or relative insulin deficiency decreases glucose utilization in muscle, fat, and liver while inducing hyperglucagonemia and hepatic glucose production Presence of a small amount of insulin prevents the development of ketosis by inhibiting lipolysis Characterized by hyperglycemia, hyperosmolality, and dehydration without ketosis More severe dehydration compared to DKA due to more gradual onset and ↑ duration of metabolic decompensation plus impaired fluid intake which is common in bedridden patients Volume contraction → renal insufficiency → ↑ hyperglycemia, ↑ osmolality → shift of fluid from neurons to ECF → mental obtundation and coma
Clinical Features	Hyperglycemia (polyuria, polydipsia, weakness) Acidosis (air hunger, nausea, vomiting, abdominal pain, Kussmaul respirations, acetone-odoured breath) Precipitating conditions (insulin omission, new diagnosis of diabetes, infection, MI, thyrotoxicosis, drugs)	Onset is insidious → preceded by weakness, polyuria, polydipsia History of decreased fluid intake History of ingesting large amounts of glucose containing fluids Dehydration (orthostatic changes) ↓ LOC → lethargy, confusion, comatose due to high serum osmolality Kussmaul respirations are absent unless the underlying precipitant has also caused a metabolic acidosis
Serum	↑ BG (typically 14-55 mmol/L, ↓ Na^+ (2° to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in Na^+ by 3 mmol/L) Normal or ↑ K^+, ↓ HCO_3^-, ↑ BUN, ↑ Cr, ketonemia, ↓ PO_4^{3-} ↑ osmolality corrected sodium = current sodium + [0.3 x (current glucose -5)] Be aware of possible euglycemic DKA (with near normal sugars) in pregnancy and with those who use SGLT2 inhibitors	↑ BG (typically 44.4-133.2 mmol/L) In mild dehydration, may have hyponatremia (spurious 2° to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in Na^+ by 3 mmol/L) – if dehydration progresses, may get hypernatremia Ketosis usually absent or mild if starvation occurs ↑ osmolality

Table 11. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

	Diabetic Ketoacidosis (DKA)	Hyperosmolar Hyperglycemic State (HHS)
ABG	Anion gap metabolic acidosis with possible 2° respiratory alkalosis If severe vomiting/dehydration there may also be a metabolic alkalosis	Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI)
Urine	+ve for glucose and ketones	-ve for ketones unless there is starvation ketosis Glycosuria
Treatment	ABCs are first priority Monitor degree of ketoacidosis with AG, not BG or serum ketone level NOTE: AG is the most important endpoint used to monitor the resolution of the metabolic acidosis Rehydration – 500 mL/h x4 h, then 250 mL/h x4 h NS if mild-moderate deficit, 1-2 L/h NS if severe deficit (shock) – Switch to 0.45% NaCl once euvolemic (continue NS if corrected $[Na^+]$ is low or rate of fall of plasma osmolality ≥3 mosm/kg/h) – Once BG reaches 14.0 mmol/L add D5W or D10W to maintain BG of 12-14 mmol/L Insulin therapy – Critical to resolve acidosis, not hyperglycemia – Do not use with hypokalemia (see below), until serum K^+ is corrected to >3.3 mmol/L – Maintain on 0.1 U/kg/h insulin R infusion – Check serum glucose hourly **K^+ replacement** – With insulin administration, hypokalemia may develop – If serum K^+ <3.3 mmol/L, give 40 mEq/L K^+ replacement and hold insulin until $[K^+]$ ≥3.3mmol/L – When K^+ 3.3-5.0 mmol/L add KCl 10-40 mEq/L to keep K^+ in the range of 3.5-5 mEq/L HCO_3^- – If pH <7.0 or if hypotension, arrhythmia, or coma is present give HCO_3^- 1 ampoule (50 mmol) in 200 mL D5W (or sterile water if available) over 1 h, repeated q1-2 h until pH ≥7.0 – Do not give if pH >7.1 (risk of metabolic alkalosis) – Can give in case of life-threatening hyperkalemia	Same resuscitation and emergency measures as DKA Rehydration – IV fluids: 1 L/h NS initially – Evaluate corrected serum Na^+ – If corrected serum Na^+ high or normal, switch to 0.45% NaCl (4-14 mL/kg/h) – If corrected serum Na^+ low, maintain NS (4-14 mL/kg/h) – When serum BG reaches 13.9 mmol/L (250 mg/dL) switch to D5W **K^+ replacement** – Less severe K^+ depletion compared to DKA – If serum K^+ <3.3 mmol/L, give 40 mEq/L K^+ replacement and hold insulin until $[K^+]$ ≥3.3mmol/L – When K^+ 3.3-5.0 mmol/L add KCL 10-40 mEq/L to keep K^+ in the range of 3.5-5 mEq/L – If serum K^+ ≥5.5 mmol/L, check K^+ every 2 h Search for precipitating event Insulin therapy – Achieved by monitoring plasma osmolality, adding glucose to infusions once BG reaches 14 mmol/L, using correct concentration of saline – Switch to 0.45% NaCl once euvolemic as urinary loss of electrolytes in osmotic diuresis are usually hypotonic – Increase saline concentration if falling too rapidly
Prognosis	<1-3.3% mortality in developed countries Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children)	Mortality rates between 12-17%, but studies looking at this included mixed DKA/HHS state

Macrovascular Complications

- increased risk of CAD, ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- CAD (see Cardiology and Cardiac Surgery, C30)
  - risk of MI is 3-5x higher in those with DM compared to age-matched controls
  - CAD is the leading cause of death in T2DM
  - most patients with DM are considered "high-risk" under the risk stratification for CAD (see *Dyslipidemias, E3*)
- ischemic stroke (see Neurology, N51)
  - risk of stroke in those with DM is approximately 2-3x higher for men and 2-5x higher for women
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - A1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Vascular Surgery, VS4)
  - manifests as intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with DM compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with DM
- screening: A1c every 3 mo, BP monitoring, lipid profile every 1-3 yr, resting ECG every 3-5 yr for high-risk patients
- treatment
  - tight blood pressure control (<130/80 mmHg), especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight LDL control (LDL ≤2.0 mmol/L) or >50% LDL reduction from baseline
  - statin use in patients with clinical CVD, age ≥40, or either diabetes duration >15 yr and age >30, or microvascular complications
  - ACEI or ARB in high-risk patients
  - smoking cessation, healthy diet, physical activity, and maintenance of healthy weight goals
  - for adults with CVD who do not meet glycemic targets, recommended to add anti-hyperglycemic agent with demonstrated cardiovascular benefit (SGLT2i/GLP-1 RAs) to reduce the risk of major CV events

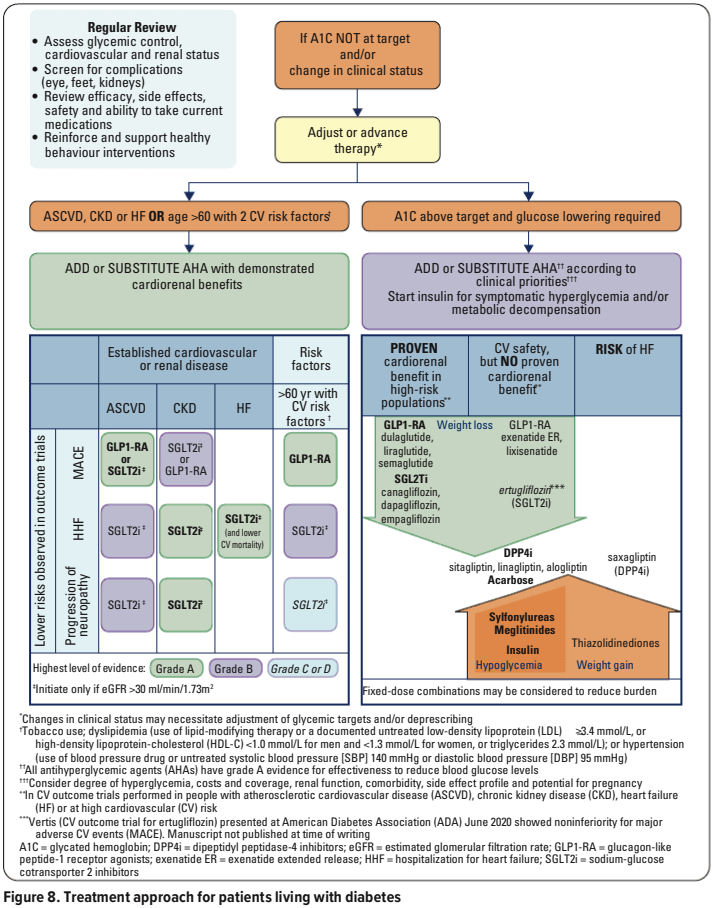
Laboratory Testing: Ketones

- The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect β-hydroxybutyrate (BHB), the ketone most frequently in excess in DKA. This has two clinical consequences:
- Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives because of the presence of BHB
- As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening when in fact they are improving

See Landmark Endocrinology Trials for more information on the Effects of ASA for Primary Prevention in Persons with Diabetes Mellitus trial. It details vascular and major bleeding events in patients with diabetes who received ASA compared to those who received a placebo.

See Landmark Endocrinology Trials table for more information on the EMPA-REG OUTCOME trial. It details the effects of empagliflozin (SGLT2 inhibitor) on cardiovascular risk in patients with T2DM.

See Landmark Endocrinology Trials table for more information on the LEADER trial. It details the effects of liraglutide (GLP-1 analogue) on cardiovascular risk in patients with T2DM.


Regular Review
• Assess glycemic control, cardiovascular and renal status
• Screen for complications (eye, feet, kidneys)
• Review efficacy, side effects, safety and ability to take current medications
• Reinforce and support healthy behaviour interventions
If A1C NOT at target and/or change in clinical status
Adjust or advance therapy*
ASCVD, CKD or HF OR age >60 with 2 CV risk factors‡
A1C above target and glucose lowering required
ADD or SUBSTITUTE AHA with demonstrated cardiorenal benefits
ADD or SUBSTITUTE AHA†† according to clinical priorities††† Start insulin for symptomatic hyperglycemia and/or metabolic decompensation
Established cardiovascular or renal disease
Risk factors
ASCVD
CKD
HF
>60 yr with CV risk factors †
Lower risks observed in outcome trials
MACE
HHF
Progression of neuropathy
GLP1-RA or SGLT2i‡
SGLT2i‡ or GLP1-RA
GLP1-RA
SGLT2i‡
SGLT2i‡
SGLT2i‡ (and lower CV mortality)
SGLT2i‡
SGLT2i‡
SGLT2i‡
SGLT2i§
Highest level of evidence: Grade A Grade B Grade C or D
‡Initiate only if eGFR >30 ml/min/1.73m²
PROVEN cardiorenal benefit in high-risk populations**
CV safety, but NO proven cardiorenal benefit*
RISK of HF
GLP1-RA dulaglutide, liraglutide, semaglutide
Weight loss
GLP1-RA exenatide ER, lixisenatide
SGL2Ti canagliflozin, dapagliflozin, empagliflozin
ertugliflozin*** (SGLT2i)
DPP4i sitagliptin, linagliptin, alogliptin
saxagliptin (DPP4i)
Acarbose
Sylfonylureas Meglitinides
Insulin
Hypoglycemia
Thiazolidinediones
Weight gain
Fixed-dose combinations may be considered to reduce burden

*Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing
‡Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) ≥3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women, or triglycerides 2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure [SBP] 140 mmHg or diastolic blood pressure [DBP] 95 mmHg)
††All antihyperglycemic agents (AHAs) have grade A evidence for effectiveness to reduce blood glucose levels
†††Consider degree of hyperglycemia, costs and coverage, renal function, comorbidity, side effect profile and potential for pregnancy
**In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk
***Vertis (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing
A1C = glycated hemoglobin; DPP4i = dipeptidyl peptidase-4 inhibitors; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon-like peptide-1 receptor agonists; exenatide ER = exenatide extended release; HHF = hospitalization for heart failure; SGLT2i = sodium-glucose cotransporter 2 inhibitors

Figure 8. Treatment approach for patients living with diabetes

Microvascular Complications

Diabetic Retinopathy (see Ophthalmology, OP34 for a more detailed description)

Epidemiology

- diabetic retinopathy is the most common cause of incident blindness in people of working age
- among individuals with T1DM, limb amputation and vision loss due to diabetic retinopathy are independent predictors of early death

Clinical Features

- macular edema: diffuse or focal vascular leakage at the macula
- non-proliferative (microaneurysms, intraretinal hemorrhage, vascular tortuosity, vascular malformation) and proliferative (abnormal vessel growth)
- retinal capillary closure

Treatment and Prevention

- tight glycemic control (delays onset, decreases progression), tight lipid control, manage HTN, smoking cessation
- ophthalmological treatments available (see Ophthalmology, OP35 for more details)
- annual follow-up visits with an optometrist or ophthalmologist to examine whether symptomatic or not through dilated pupils (immediate referral after diagnosis of T2DM; 5 yr after diagnosis of T1DM for those ≥15 yr)
- interval for follow up should be tailored to severity of retinopathy

Diabetic Nephropathy (see Nephrology, NP34 for a more detailed description)

Epidemiology
- DM-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with T1DM (after 5-10 yr) and 4-20% with T2DM have progressive nephropathy

Screening
- serum creatinine for eGFR, random urine ACR
- ACR is used as albuminuria is considered the earliest clinical sign of diabetic nephropathy (microalbuminuria); diagnosis requires persistent elevated urinary albumin (2 out of 3 urinary samples required over 3 mo)
- 24 h urine collection for protein/albumin is the gold standard but is difficult to perform, inconvenient, and often incorrect; random urine albumin is insufficient as albumin levels vary with urine concentration
- begin screening annually at diagnosis for all T2DM, and >5 yr after diagnosis of T1DM for postpubertal patients

Treatment and Prevention
- appropriate glycemic control
- appropriate BP control (<130/80 mmHg)
- use either ACEI or ARB to delay progression of CKD (often used first line for CVD protection)
- use SGLT2i for nephroprotection
- limit use of nephrotoxic drugs and dyes

See Landmark Endocrinology Trials table for more information on the Steno-2 trial. It details the effects of intensive, multifactorial interventions on the rates of death in patients with T2DM and microalbuminuria

Diabetic Neuropathy

Epidemiology
- approximately 50% of patients within 10 yr of T1DM and T2DM onset

Pathophysiology
- can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy
- mechanism poorly understood
- acute cranial nerve (CN) palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerves
- the more common motor and sensory neuropathies are thought to be related to metabolic, vascular, and possibly hormonal factors

Screening
- 128 Hz tuning fork or 10 g monofilament
- begin screening annually at diagnosis for all T2DM, and >5 yr after diagnosis of T1DM for post-pubertal patients

Clinical Features

Table 12. Clinical Features of Diabetic Neuropathies

Peripheral Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands Decreased ankle reflex Distal-predominant as the longest nerves are affected first Classic stocking-glove distribution May result in neuropathic ulceration of foot	Less common than sensory neuropathy and occurs later in the disease process Delayed motor nerve conduction and muscle weakness/atrophy May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex) Some of the motor neuropathies spontaneously resolve after 6-8 wk Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell's palsy) Diabetic amyotrophy i.e. Bruns-Garland Syndrome: refers to pain, weakness, and wasting of hip flexors or extensors	Postural hypotension, tachycardia, decreased cardiovascular response to valsalva maneuver Gastroparesis and alternating diarrhea and constipation Urinary retention and erectile dysfunction

Treatment and Management
- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anticonvulsants (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with dietary modification, domperidone and/or metoclopramide (dopamine antagonists), erythromycin (motilin receptor agonist)
- medical, mechanical, and surgical treatment for erectile dysfunction (see Urology, U33)

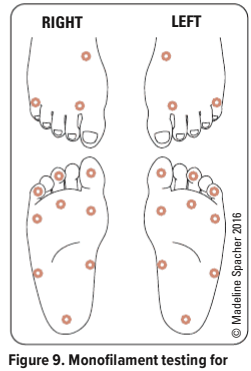


Figure 9. Monofilament testing for diabetic neuropathy

Pharmacologic Interventions for Painful Diabetic Neuropathy: An Umbrella Systematic Review and Comparative Effectiveness Network Meta-Analysis
Ann Intern Med 2014;161:639-49
Purpose: To compare the efficacies of various oral and topical analgesics for diabetic neuropathy.
Study Selection: RCTs that assessed pharmacologic treatments for painful diabetic peripheral neuropathy in adults.
Results: 65 RCTs involving 12632 patients were included. The following pharmacological agents demonstrated superiority over placebo for short-term pain control: serotonin and norepinephrine reuptake inhibitors (SNRIs) (standardized mean difference (SMD), -1.36; 95% credible interval (CrI), [-1.77 to -0.95]), topical capsaicin (SMD, -0.91; CrI [-1.18 to -0.08]), tricyclic antidepressants (TCAs) (SMD, -0.78; CrI [-1.24 to -0.33]), and anticonvulsants (SMD, -0.67; CrI [-0.97 to -0.37]). Specific agents included: carbamazepine (SMD, -1.57; CrI [-2.83 to -0.31]), venlafaxine (SMD, -1.53; CrI [-2.41 to -0.65]), duloxetine (SMD, -1.33; CrI [-1.82 to -0.86]), and amitriptyline (SMD, -0.72; CrI [-1.35 to -0.08]).
Conclusion: SNRIs, topical capsaicin, TCAs and anticonvulsants are effective in short-term management of painful diabetic neuropathy, but their relative efficacy compared to each other is unknown.

Other Complications

Dermatologic
- diabetic dermopathy: atrophic brown spots commonly in pretibial region ("tibia spots") secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

Bone and Joint Disease
- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren's contracture
- increased fracture risk in both T1DM and T2DM due to decreased bone quality
- adhesive capsulitis ("frozen shoulder")

Cataracts
- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

Infections
- see *Infectious Diseases, Diabetic Foot Infections, ID14*

Hypoglycemia

Etiology and Pathophysiology
- hypoglycemia occurs most frequently in people with DM receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without DM, care must be taken to distinguish hypoglycemia that occurs in critically ill or medicated patients from hypoglycemia that presents in individuals who are seemingly well
  - each invokes a separate DDx
  - the timing of hypoglycemia may also provide a clue to the diagnosis (e.g. individuals with an insulinoma typically have fasting hypoglycemia whereas those with non-insulinoma pancreatogenous hypoglycemia experience predominantly postprandial hypoglycemia)
  - must be distinguished from pseudohypoglycemia, defined as situations in which either BG >3.9 mmol/L with clinical signs of hypoglycemia (e.g. fatigue, headache, visual disturbances, or lightheadedness) or BG <3.9 mmol/L but patient is asymptomatic

Table 13. Causes of Hypoglycemia

Insulin-Dependent Causes	Insulin-Independent Causes
Exogenous insulin	Hepatic failure
Sulfonylurea or meglitinide	Renal failure
Pentamidine (possibly due to β-cell destruction resulting in insulin release)	Inanition
Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor)	Hormone deficiency (cortisol, glucagon, and epinephrine in insulin-deficient DM)
Insulinoma	Non-islet cell tumours (typically the result of mesenchymal tumour overproduction of IGF-2)
Non-insulinoma pancreatogenous hypoglycemia	Inborn error of carbohydrate metabolism, glycogen storage disease, gluconeogenic enzyme
Post-gastric bypass hypoglycemia	Alcohol
	Drugs (e.g. quinine, indomethacin, gatifloxacin, lithium, ACEI, β-adrenergic receptor blockers)

Clinical Features
- Whipple's triad – suggests a patient's symptoms are from hypoglycemia
  1. serum glucose <4.0 mmol/L
  2. neuroglycopenic symptoms (below)
  3. rapid relief provided by administration of glucose
- autonomic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia, hunger
- neuroglycopenic symptoms (caused by brain glucose deprivation)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations
- depend on a thorough history, physical exam, and available biochemical investigations as these may provide clues to the etiology of hypoglycemia
  - for example, if suspecting insulin and insulin secretagogues in patients with diabetes, assess for cortisol deficiency. In a patient with weight loss, hyperpigmentation, and hyperkalemia, consider the possibility of IGF-2 mediated hypoglycemia. In an individual with a gastrointestinal stromal tumour (GIST), think about renal/hepatic failure in the setting of critical illness

Other Players in Glucose Homeostasis
These hormones act to increase:
Blood glucose levels
Glucagon
Epinephrine
Cortisol
Growth hormone

C-Peptide
A short peptide released into the circulation when proinsulin is cleaved to insulin

Use of C-peptide Levels to Distinguish between Exogenous and Endogenous Source of Hyperinsulinemia
Increased = endogenous
Decreased or normal = exogenous

Treatment of an Acute Hypoglycemic Episode (Blood Glucose <4.0 mmol/L) in the Awake Patient (e.g. able to self-treat)

1) Eat 15 g of rapid-acting carbohydrates (e.g. 3 packets of sugar dissolved in water; 3/4 cup of juice)
↓
2) Wait 15 min
↓
3) Retest BG
↓
4) Repeat steps 1-3 until BG >5 mmol/L
↓
5) Eat next scheduled meal. If next meal is >1 h away, eat snack including 15 g of carbohydrate and protein

Hypoglycemia Unawareness (T1DM >>> T2DM)
- Patient remains asymptomatic until severe hypoglycemic levels are reached
- Often occurs after repeated episodes of hypoglycemia as the patient develops blunted/minimal autonomic response
- **Causes:**
  - Decreased glucagon/epinephrine response
  - History of repeated hypoglycemia or low A1c
  - Autonomic neuropathy
- May not be safe for patient to drive
- Suggest that patient obtain a Medic-Alert™ bracelet if at risk for hypoglycemia, especially with hypoglycemia unawareness and consider use of advanced monitoring systems (continuous glucose monitor, flash glucose monitor)

Refer to Diabetes Canada 2018 guidelines for advice around diabetes and driving

- when the cause of hypoglycemia is not evident, screen for oral hypoglycemic agents (ideally all available sulfonylureas and glinides) and measure plasma glucose, insulin, proinsulin, C-peptide, b-hydroxybutyrate, and insulin Ab during a spontaneous hypoglycemic episode or a supervised fast of up to 72 h. If hypoglycemia occurs only in the postprandial state, evaluate the patient first with a mixed meal test
- correct hypoglycemia with injection of 1.0 mg glucagon IV with measurement of plasma glucose response. This will distinguish endogenous and exogenous hyperinsulinism from other causes of hypoglycemia

Treatment

- for tumoural hypoglycemia, definitive treatment requires resection of the tumour. If that is not possible, certain medications can be helpful such as diazoxide for patients with insulinoma
  - for non-insulinoma pancreatogenous hypoglycemia and post-bariatric bypass hypoglycemia, dietary changes including reducing the amount of carbohydrate intake and small frequent meals may be helpful. For patients who do not respond to nutritional modification or have severe symptoms, acarbose can be utilized
- see Emergency Medicine, ER35
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV in 1-3 min or 1 mg glucagon SC or IM (if no IV access is available)
  - may need ongoing glucose infusion once BG >5 mmol/L

Metabolic Syndrome

- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, HTN, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include DM, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Features of Metabolic Syndrome (≥3 measures to make a Dx)

Measure	Men	Women
Abdominal Obesity (Elevated Waist Circumference)		
Canada, USA	≥102 cm (40 inches)	≥88 cm (35 inches)
Europid, Middle Eastern, Sub-Saharan Africa, Mediterranean	≥94 cm (37 inches)	≥80 cm (31.5 inches)
Asian, Japanese, South & Central America	≥90 cm (35 inches)	≥80 cm (31.5 inches)
TG Level	≥1.7 mmol/L (150 mg/dL)	
HDL-C Level	<1.0 mmol/L (<40 mg/dL)	<1.3 mmol/L (<50 mg/dL)
Blood Pressure	≥130/85 mmHg	
Fasting Glucose Level	≥5.6 mmol/L (>100 mg/dL)	

Drug treatment for any elevated marker is an alternate indicator

Obesity

- see Family Medicine, FM9

Pituitary Gland

Pituitary Hormones

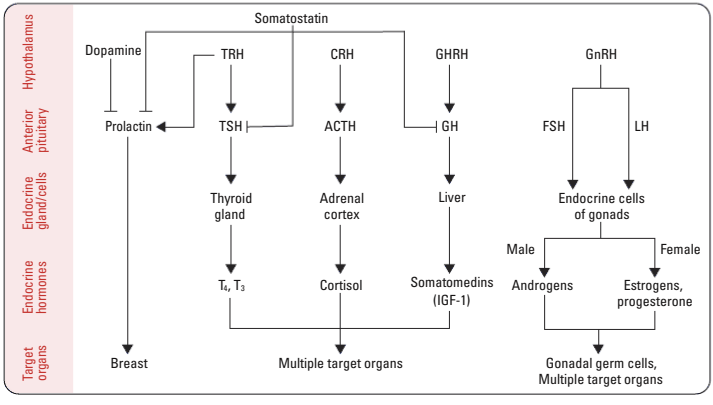


Figure 10. Hypothalamic-pituitary hormonal axes

Hypothalamic Control of Pituitary

- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except PRL, which is primarily under inhibitory control by dopamine. GH and TSH are stimulated by GHRH and TRH respectively while inhibition by somatostatin is less important for control
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of PRL and hyposecretion of all remaining hormones

Anterior Pituitary Hormones

- FSH, LH, ACTH, TSH, GH, PRL
  - sequential loss of anterior pituitary hormones due to mass effect: GH, LH, FSH, TSH, ACTH, PRL ("Go Look For the Adenoma Please")
- these hormones are produced, stored, and released from the anterior pituitary but regulated by hormones produced by the hypothalamus

Posterior Pituitary (Hypothalamic) Hormones

- ADH and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus, these hormones are stored in and released from the posterior pituitary

Table 14. The Physiology and Action of Pituitary Hormones

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
LH/FSH	Stimulate gonads via cAMP Ovary: LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles FSH: growth of granulosa cells in ovarian follicle; controls estrogen production Testes: LH: production of testosterone (Leydig cells) FSH: production of spermatozoa (Sertoli cells)	Polypeptide Glycoproteins (same α subunit as TSH and hCG) Secreted in pulsatile fashion	Estrogen Progesterone Testosterone Inhibin Continuous (i.e. non-pulsatile) GnRH infusion	Pulsatile GnRH (low frequency pulsation = FSH release, high frequency pulsation = LH release)
ACTH	Stimulates growth of adrenal cortex and secretion of its hormones via cAMP	Polypeptide Circadian rhythm (highest in the morning, lowest at midnight)	Dexamethasone, cortisol, and other glucocorticoids	Corticotropin-Releasing Hormone Metyrapone hypoglycemia Vasopressin Fever, pain, stress
TSH	Stimulates growth of thyroid and secretion of T4 and T3 via cAMP	Glycoprotein Note: hCG can activate the TSH receptor and therefore have thyroid-stimulating activity	Thyroid hormones (T4 and T3) and analogues, dopamine, somatostatin, cytokines, high dose glucocorticoids	TRH AVP α adrenergic agonist
PRL	Promotes milk production and breast tissue development Inhibits gonadotropin secretion	Polypeptide Episodic secretion	Dopamine (only pituitary hormone under tonic inhibition of secretion)	Sleep Stress, hypoglycemia Pregnancy, breastfeeding Mid-menstrual cycle Sexual activity TRH (primary hypothyroidism) Drugs: antipsychotics, tricyclic antidepressants, metoclopramide, domperidone, verapamil, methyldopa, opioids, high dose estrogen
GH	Has direct effects on peripheral target cells Needed for linear growth and also has metabolic effects to increase serum glucose Stimulates secretion of IGF-1 by the liver, a potent growth and differentiation factor	Polypeptide Acts indirectly through IGF-1 (somatomedin-C) synthesized in the liver and has direct effects Serum GH undetectable for most of the day and suppressed after meals high in glucose Sustained rise during sleep	Glucose challenge Glucocorticoids Somatostatin Dopamine D2 receptor agonists in some GH-secreting tumours IGF-1 (long-loop)	GHRH Insulin-induced hypoglycemia Ghrelin Exercise REM sleep Arginine, clonidine, propranolol, L-dopa Sex hormones Dopamine agonists in normal individuals
ADH	Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine	Octapeptide Secreted by posterior pituitary Osmoreceptors in hypothalamus detect serum osmolality Contracted plasma volume detected by baroreceptors is a more potent stimulus than ↑ osmolality	↓ serum osmolality	Hypovolemia or ↓ effective circulatory volume ↑ serum osmolality Stress, pain, fever, system CNS disorders
Oxytocin	Causes uterine contraction Breast milk secretion	Nonapeptide Secreted by posterior pituitary	EtOH	Suckling Distention of female genital tract during labour via stretch receptors

Growth Hormone

GH Deficiency
- cause of short stature in children (see Pediatrics, P34)
- adults exhibit increased fat and decreased lean body mass, decreased bone mineral density, and fatigue
- diagnosis made with low serum IGF-1 levels in individuals with deficiencies in three or more pituitary axes, or by failure to increase GH with a provocative test (see above under GH secretory stimulus); insulin tolerance test to induce hypoglycemia is the gold standard dynamic test
- Tx: GH replacement is not always indicated after max linear height and peak bone mass is reached; consider in an adult patient with childhood onset irreversible GH deficiency (some children who are diagnosed with idiopathic GH deficiency will have normal GH responses when tested as adults and do not require GH treatment). GH replacement can also be provided to patients with adult onset GH deficiency who do not have an active malignancy and prefer treatment after a discussion about its potential benefits, adverse effects, and cost

GH Excess

Etiology
- GH secreting pituitary adenoma, neuroendocrine tumours secreting ectopic GH or GHRH (very rare)

Pathophysiology
- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in GH excess states, secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

Clinical Features
- leads to gigantism in children (before epiphyseal fusion)
- leads to acromegaly in adults (after epiphyseal fusion)
- dermatologic (thickening of skin, increased sebum production, sweating, acne, sebaceous cysts), musculoskeletal (enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, carpal tunnel syndrome, osteoarthritis), cardiometabolic (HTN, DM, acanthosis nigricans, cardiomyopathy), sleep apnea, sexual (low libido)

Investigations
- first line test: serum IGF-1 (expected to be elevated)
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- CT, MRI, or skull x-rays may show cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica
- MRI of the sella turcica is needed to look for a tumour

Treatment
- surgery is the recommended initial therapy for the majority of patients with acromegaly; second line options include somatostatin analogue (octreotide), dopamine agonist (cabergoline), GH receptor antagonist (pegvisomant), radiation
  - radiation may be considered in patients whose disease is not controlled by surgery or medical treatment

Risks Associated with GH Excess
- Cardiac disease (e.g. cardiomyopathy, valvulopathy, arrhythmias, CAD) in 1/3 of patients
- Two-fold increase in mortality in acromegaly due to acromegaly-associated complications such as HTN, diabetes, CVD, and cerebrovascular disease
- Increased risk of OSA
- HTN in 1/3 of patients
- Increased risk of cancer (particularly colon cancer)

Prolactin

Hyperprolactinemia

Etiology
- prolactinoma: most common pituitary adenoma
- pituitary stalk compression: from sellar masses or damage causing reduced dopamine inhibition of PRL release
- primary hypothyroidism (increased TRH), PCOS, acromegaly
- decreased clearance due to CKD or severe liver disease (PRL is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high PRL levels: antipsychotics (common), antidepressants, antihypertensives (verapamil/methyldopa), bowel motility agents (metoclopramide/domperidone), H2-blockers, opiates (morphine), estrogens (e.g. oral contraceptives)
- macroprolactinemia (high molecular weight PRL also known as big-big PRL) that has no action but results in falsely elevated serum prolactin
- physiologic causes: pregnancy, stress, sleep, nipple stimulation, factors affecting the chest wall

Clinical Features
- galactorrhea (secretion of breast milk in women and, in rare cases, men), infertility, hypogonadism, amenorrhea, oligomenorrhea, erectile dysfunction

Approach to Nipple Discharge
- Differentiate between galactorrhea (fat droplets present) vs. breast discharge (usually unilateral, may be bloody or serous)
- If galactorrhea, determine if physiologic (e.g. pregnancy, lactation) vs. pathologic
- If abnormal breast discharge, must rule out a breast malignancy

Investigations
- serum PRL, TSH, liver enzyme tests, creatinine, hCG in all women of reproductive age
- macroprolactin level in patients with hyperprolactinemia but no symptoms of PRL excess
- MRI of the sella turcica when a secondary cause is not identified or when PRL levels suggest that there may be underlying tumoural hyperprolactinemia

Treatment
- first line: dopamine agonists (bromocriptine, cabergoline, quinagolide)
- surgery ± radiation (rare)
- PRL-secreting tumours are often slow-growing; treatment may not be necessary in the setting of small tumours associated with hyperprolactinemia which does not result in hypogonadism or bothersome galactorrhea
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline
J Clin Endocr Metab 2011;96:273-88
- Indications to treat:
  - Symptomatic patients, in particular those with galactorrhea, hypogonadism-amenorrhea, low libido, or infertility
  - Adenomas ≥1 cm or any size causing structural compression
- For patients with symptomatic prolactinomas, dopamine agonist therapy should be used to lower prolactin levels, decrease tumour size, and restore gonadal function
- Cabergoline should be preferentially used due to higher efficacy in normalizing PRL levels and shrinking pituitary tumours
- For symptomatic patients with treatment-resistant prolactinomas, increase the dose to maximal tolerable dose before referring for surgery
- Most women with prolactinomas should discontinue dopamine agonist therapy immediately if they become pregnant (except for patients with large invasive tumours)

Thyroid Stimulating Hormone
- see *Thyroid, E24*

Adrenocorticotropic Hormone
- see *Adrenal Cortex, E33*

Luteinizing Hormone and Follicle Stimulating Hormone

Hypogonadotropic Hypogonadism
- hypogonadism due to impaired release of FSH and LH, causing low FSH, low LH, low estrogen and testosterone

Etiology
- congenital: Kallmann syndrome, CHARGE syndrome, GnRH insensitivity
- secondary: CNS or pituitary tumours, pituitary apoplexy, hypothalamic-pituitary radiation, drugs (GnRH agonists/antagonists, glucocorticoids, narcotics, chemotherapy, drugs causing hyperprolactinemia, opioids), functional deficiency due to another cause (hyperprolactinemia, chronic systemic illnesses, eating disorders, hypothyroidism, DM, Cushing's disease), systemic diseases involving the hypothalamus/pituitary (hemochromatosis, sarcoidosis, histiocytosis)

Clinical Features
- amenorrhea, low libido, decrease in energy, erectile dysfunction (see Urology, U33), loss of body hair, thin skin, testicular atrophy, decrease in muscle mass, failure of pubertal development (if developed before puberty)

Treatment
- treat underlying cause if present
- combined FSH/LH hormone therapy, hCG, recombinant FSH, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

Hypergonadotropic Hypogonadism
- hypogonadism due to impaired response of the gonads to FSH and LH; pts have high FSH/high LH and low estrogen or testosterone

Etiology
- congenital:
  - chromosomal abnormalities (Turner's syndrome, Klinefelter syndrome, XX gonadal dysgenesis)
  - enzyme defects (17α-hydroxylase deficiency, 17,20-lyase deficiency)
  - gonadotropin resistance (Leydig cell hypoplasia, FSH insensitivity, pseudohypoparathyroidism type 1A)
- acquired:
  - gonadal toxins (chemotherapy, radiation)
  - drugs (antiandrogens, alcohol)
  - infections (STIs, mumps)
  - gonadal failure in adults (androgen decline and testicular failure in men, premature ovarian insufficiency and menopause in women)

Clinical Features
- amenorrhea, erectile dysfunction (see Urology, U33, loss of body hair, fine skin, testicular atrophy, failure of pubertal development, low libido, decrease in energy, and infertility

Treatment
- hormone replacement therapy consisting of androgen (for males) and estrogen and progesterone (for females) administration

Antidiuretic Hormone

Diabetes Insipidus (see Nephrology, NP12)

Definition
- disorder of ineffective ADH (decreased production or peripheral resistance) resulting in passage of large volumes of dilute urine

Etiology and Pathophysiology
- central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, infiltration or lesion of the stalk, hydrocephalus, Langerhans cell histiocytosis, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, CKD, hereditary nephrogenic DI
- psychogenic polydipsia and osmotic diuresis must be ruled out

Clinical Features
- passage of large volumes of dilute urine (>3L/day), polydipsia, and dehydration; hypernatremia can develop with inadequate water consumption or secondary to an impaired thirst mechanism (hypernatremia not necessary for diagnosis)
- central DI: visual field defect, headache, other neurological features, or evidence of other pituitary hormone deficiencies may be present

Diagnosing Subtypes of Diabetes Insipidus with Desmopressin Response

Concentrated urine = **C**entral
No effect = **N**ephrogenic

Diagnostic Criteria
- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic polydipsia
- response to exogenous ADH (DDAVP) will distinguish central DI from nephrogenic DI

Treatment
- central DI: first line = desmopressin; second line = chlorpropamide, thiazides, NSAIDs, and carbamazepine
- nephrogenic DI: solute restriction, thiazide diuretics

Syndrome of inappropriate ADH secretion (SIADH) vs. Cerebral Salt Wasting (CSW)
CSW can occur in cases of subarachnoid hemorrhage. Na^+ is excreted by malfunctioning renal tubules, mimicking findings of SIADH; hallmark is hypovolemia

Syndrome of Inappropriate ADH Secretion

Diagnostic Criteria
- 1) hyponatremia (serum Na^+<135 mEq/L) with 2) plasma hypo-osmolality (<275 mOsm/kg), 3) urine Na^+concentration >40 mEq/L, 4) urine osmolality >100 mOsm/kg), 5) euvolemia (no edema), and 6) absence of adrenal, renal, or thyroid insufficiency

Etiology and Pathophysiology
- stress (post-surgical)
- malignancy (ectopic ADH production by tumours including small cell carcinoma of the lung, extrapulmonary small cell carcinomas, squamous cell carcinoma of the head and neck)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
- respiratory disease (tuberculosis, pneumonia, empyema)
- drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

Clinical Features
- symptoms of hyponatremia: headaches, nausea, vomiting, muscle cramps, tremors, cerebral edema if severe (confusion, mood swings, hallucinations, seizures, coma)

Treatment
- goal is to increase serum sodium
- treat underlying cause, fluid restriction (800-1000 mL/d), vasopressin receptor antagonists (tolvaptan, conivaptan), and furosemide

Pituitary Pathology

Pituitary Adenoma (see Neurosurgery, NS18)

Clinical Features

- local mass effects
- visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies; rare), loss of colour vision, headaches; increased ICP is rare
- hypofunction
- hypopituitarism
- hyperfunction
- PRL (galactorrhea, hypogonadism), GH (acromegaly in adults, gigantism in children), ACTH (Cushing's disease = Cushing's syndrome caused by a pituitary tumour)
- tumours secreting TSH are rare

Investigations

- radiological evaluation (MRI sella is imaging of choice)
- formal visual field testing for tumours compressing the optic chiasm
- laboratory tests of hypothalamic-pituitary hormonal function

Important Deficiencies to Recognize are:

Adrenal insufficiency

Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis

Hypopituitarism

Etiology (The Eight I's)

- **I**nvasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke's cleft, arachnoid, or dermoid), metastases
- **I**nfarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive postpartum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache, and altered LOC; can be fatal if not recognized and treated early)
- **I**nfiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- **I**nfectious
  - syphilis, tuberculosis, fungal (histoplasmosis), parasitic (toxoplasmosis)
- **I**njury
  - severe head trauma
- **I**mmunologic
  - autoimmune destruction (hypophysitis)
- **I**atrogenic
  - following surgery, radiation, or medications (immunotherapy)
- **I**diopathic
  - familial forms, congenital midline defects

The Pituitary Hormones

Compression of the pituitary by a mass leads to loss of pituitary hormones in the following usual order:

"**G**o **L**ook **F**or **T**he **A**denoma **P**lease"

GH, **L**H, **F**SH, **T**SH, **A**CTH, **P**RL + posterior pituitary hormones: ADH and oxytocin

Clinical Features

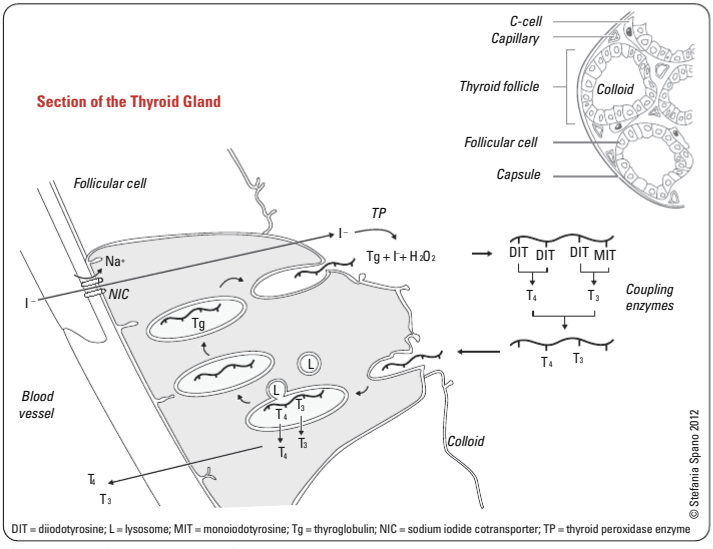
- symptoms depend on which hormone is deficient:
  - ACTH (central adrenal insufficiency): fatigue, weight loss, hypoglycemia, anemia, hyponatremia, failure to thrive, and delayed puberty in children
  - GH: short stature in children; adults exhibit increased fat and decreased lean body mass, decreased BMD, fatigue
  - TSH (central hypothyroidism): tiredness, cold intolerance, constipation, weight gain
  - LH and FSH (hypogonadotropic hypogonadism): oligo- or amenorrhea, infertility, decreased facial/body hair and muscle mass in men, erectile dysfunction, delayed puberty
  - Prolactin: usually asymptomatic, inability to breastfeed
  - ADH: symptoms of DI (extreme thirst, polydipsia, hypernatremia)
  - Oxytocin: usually asymptomatic – only needed during labour and breastfeeding

Investigations

- 8 am cortisol, PRL, TSH, Free T4, LH, FSH, Estradiol or Testosterone, GH, IGF-1, Na**I**, Osmolality
- initial test if 8 am is low/borderline: cosyntropin stimulation test (if results equivocal, proceed to insulin tolerance test)
- insulin tolerance test: insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and cortisol (normal response)
- triple bolus test (rarely done)

Thyroid

Thyroid Hormones



DIT = diiodotyrosine; L = lysosome; MIT = monoiodotyrosine; Tg = thyroglobulin; NIC = sodium iodide cotransporter; TP = thyroid peroxidase enzyme

Figure 11. Thyroid hormone synthesis

Synthetic Function of the Thyroid Gland

- the synthesis of thyroid hormones T4 and T3 by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, proteolysis of thyroglobulin, and release of T4 and T3
  - more than 90% of thyroid hormone secreted by the thyroid is T4
- free T4 (0.02%) and free T3 (0.3%) represent the hormonally active fraction of thyroid hormones
  - the remaining fraction is bound to TBG, albumin, and transthyretin, and is biologically inactive
- T3 is more biologically active (approximately 4x as potent as T4), but T3 is present in the blood in smaller quantities and has a shorter half-life compared to T4
- 85% of T4 is converted to T3 or reverse T3 in the periphery by deiodinase enzymes
- reverse T3 is metabolically inactive but produced in times of stress to decrease metabolic activity
- most of the plasma T3 pool is derived from the peripheral conversion of T4
- calcitonin, a peptide hormone, is also produced in the thyroid by the parafollicular cells (C cells)
  - calcitonin functions by inhibiting osteoclast activity and increasing renal calcium excretion

Role of Thyroid Hormones

- thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
- diffuse actions, affecting nearly every organ system
- tissue-specific effects determined by the expression of the types of thyroid receptor isoform and the local production of T3
- increase basal metabolic rate through increased Na^+/K^+ATPase activity, increased O_2 consumption, increased respiration, heat generation, and increased cardiovascular activity
- when present at higher than normal levels, potentiate the actions of GH, catecholamines (epinephrine, norepinephrine), glucagon, and cortisol, resulting in increased gluconeogenesis, ketogenesis, and proteolysis, mimicking what happens in starvation
- increase sensitivity to catecholamines by up-regulating their receptors, but do not alter their blood concentrations
- required for normal growth in the fetus and child, including the CNS, via stimulation of GH release, in synergism with cortisol

Regulation of Thyroid Function

- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators); the negative feedback mechanism of T3 acts on the anterior pituitary to inhibit TSH and on the hypothalamus to inhibit TRH

Extra-Thyroidal Factors Impacting Thyroid Hormone Homeostasis: A Review
JRM 2015;4(1):40-49

- Most peripheral thyroid metabolism occurs in the liver and kidneys, thus severe liver disease and CKD can significantly alter the T3:T4 ratio.
- Alcohol dependence results in hypothalamic-pituitary-thyroid axis dysfunction demonstrated by decreased TSH, T4, and T3 levels.
- Smoking is associated with lower TSH levels in a dose-dependent manner, with heavy smokers (8-12 cigarettes/d) being associated with more TSH suppression than light smokers (<4 cigarettes/d).
- Heavy metal exposure including lead, mercury, and cadmium has been shown to alter thyroid hormone function and peripheral metabolism.

Patterns of Hormone Levels

	TSH	T_3, T_4
1° Hyper	↓	↑
2° Hyper	↑	↑
1° Hypo	↑	↓
2° Hypo	↓	↓

- T3 intrathyroid (autoregulation)
  - synthesis (Wolff-Chaikoff effect, Jod-Basedow effect)
  - varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T3 to T4 in iodide deficiency
  - increased activity of peripheral 5'-deiodinase in hypothyroidism increases T3 production despite low T4 levels

Tests of Thyroid Function and Structure

TSH
- third generation TSH is the best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low because of negative feedback from increased levels of circulating T4 and T3
  - secondary: increased TSH results in increased T4 and T3
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from T4 and T3
  - secondary: TSH is low or inappropriately normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T4 and Free T3
- standard assessment of thyroid function measures TSH and, if necessary, free T4. Free T3 should only be measured in the small subset of patients with hyperthyroidism and suspected T3 toxicosis. In this case, TSH would be suppressed, free T4 normal, and free T3 elevated

Thyroid Autoantibodies
- TgAb, TPOAb, and TRAb of the blocking variety are increased in Hashimoto's disease; normal variant in 10-20% of individuals
- TRAb of the stimulating variety are also referred to as TSI and can cause Graves' disease. TRAb receptor blocking and stimulating antibodies are seen in patients with Graves' disease

Plasma Thyroglobulin
- used to monitor for residual thyroid tissue post-thyroidectomy, e.g. tumour marker for thyroid cancer recurrence
- detectable or elevated levels may suggest persistent, recurrent, or metastatic disease
- assay can be impacted by the presence of TgAb. Therefore, both must be tested to ensure accurate thyroglobulin results

Serum Calcitonin
- not routinely done to investigate thyroid nodules
- ordered if suspicion of MTC (e.g. in patients with a thyroid nodule and suspected or confirmed MEN 2A or 2B syndromes or those who have a pathogenic mutation in *RET* gene)
- used to monitor for residual or recurrent MTC

Thyroid Imaging/Scans
- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
  - to measure size of gland, characterize thyroid nodules, facilitate FNA biopsy (FNAB)
  - U/S is the first line tool for identification of thyroid nodules that require FNAB; exception is hyperthyroid patients with thyroid nodules where use of a radioisotope thyroid scan and RAIU (see below) permits identification of hyperfunctioning nodules, which generally do not need to be biopsied
- radioisotope thyroid scan (Technetium-99) only if 1) one or more thyroid nodule(s) and 2) patient is hyperthyroid to determine whether nodules are hot (functioning → excess thyroid hormone production) or cold (non-functioning)
- hot nodule → very low chance of malignancy; treat hyperthyroidism
- cold nodule → further workup required (U/S, then FNAB if concerning sonographic features)
- RAIU
  - test of function: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland in vivo
  - if ↑ uptake (e.g. incorporated), gland is overproducing thyroid hormone (hyperthyroid)
  - if ↓ uptake (e.g. not incorporated), gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)
- see *Figure 12, E33* for further information regarding the utility of these scans

Thyroid Biopsy
- FNA for cytology
  - differentiates between benign and malignant disease
  - best done under U/S guidance
  - accuracy decreased if nodule is greater than 50% cystic, or if nodule is located posteriorly in the gland

Thyroid Assessment
- TSH
- Serum free thyroid hormones (T_4, T_3)
- Antibodies (TRAb, TgAb, and TPOAb)
- Thyroglobulin (to monitor thyroid cancer)
- Thyroid U/S when there is a palpable thyroid abnormality or suspected thyroid mass
- Nuclear uptake and scan (for hyperthyroidism)
- Biopsy (FNA) of thyroid nodules warranting a cytological evaluation

Does this Patient have a Goitre?
From The Rational Clinical Examination
JAMA 2009; https://jamaevidence.mhmedical.com/content.aspx?bookid=845&sectionid=61357508
Study: Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of a goitre.
Results: Clinical diagnosis was based on degree of lateral prominence, visibility, and palpability of the thyroid gland. No evidence exists to support the superiority of any one method.
The combined results of 4 studies detail the predictive utility of assessing grades of thyroid gland weight:

Weight	Reference	LR+	95% CI
0-20 g	Normal	0.15	(0.10-0.21)
20-40 g	1-2x	1.9	(1.1-3.0)
>40 g	>2x	25.0	(2.6-175)

Alternatively, defining a goitre as a mass larger than the distal phalanx of the thumb has been shown to have an LR+ of 3.0 (95% CI 2.5-3.5) and LR- of 0.30 (95% CI: 0.24-0.37) in children, and an LR+ of 4.7 (95% CI 3.6-6.0) and LR- of 0.08 (95% CI 0.02-0.27) for the presence of a goitre.
Conclusions: Use of weight of thyroid tissue is an appropriate method of diagnosing a goitre, while comparing the size of the thyroid mass to the distal phalanx of the thumb may be a useful alternative.

Table 15. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

	Hyperthyroidism	Hypothyroidism
TSH	Decreased in 1° hyperthyroidism Increased in 2° hyperthyroidism	Increased in 1° hypothyroidism Decreased in 2° hypothyroidism
Free T_4	Increased in 1° hyperthyroidism Increased in 2° hyperthyroidism	Decreased in 1° hypothyroidism Decreased in 2° hypothyroidism
Antibodies	Graves': TRAb	Hashimoto's: TPOAb, TgAb
RAIU	Increased uptake Graves' Toxic multinodular goitre Toxic adenoma	Decreased uptake Subacute thyroiditis Recent iodine load Exogenous thyroid hormone
Radioisotope Thyroid Scan	Graves': homogenous diffuse uptake Multinodular goitre: heterogeneous uptake Toxic adenoma: single intense area of uptake with suppression elsewhere	

Drugs Affecting Thyroid Function

Montanelli, L., Benvenga, S., Hegedüs, L., Vitti, P., Latrofa, F., Duntas, L.H. Endocrinology. Springer, Cham. c2018. Drugs and Other Substances Interfering with Thyroid Function; p733-761

(a) Lithium
(b) Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)
(c) Antiepileptics
(d) Rifampin
(e) Metformin
(f) Amiodarone

Thyrotoxicosis

Definition

- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

Epidemiology

- 1% of general population have hyperthyroidism
- F:M=5:1

Etiology and Pathophysiology

Table 16. Differential Diagnosis of Thyrotoxicosis

Disorder	TSH	Free T_4/T_3	Thyroid Antibodies	RAIU	Other
HYPERTHYROIDISM					
Graves' Disease	Decreased	Increased	TRAb	Increased	Homogeneous diffuse uptake on scan
Toxic Nodular Goitre	Decreased	Increased	None	Increased	Heterogeneous uptake on scan
Toxic Nodule	Decreased	Increased	None	Increased	Intense uptake in hot nodule on scan with suppressed uptake in the rest of the gland
THYROIDITIS					
Subacute, Silent, Postpartum	Decreased	Increased	Up to 50% of cases (TPOAb, TgAb)	Decreased (increases once entering hypothyroid phase, when TSH rises)	In classical subacute painful thyroiditis, ESR increased
EXTRATHYROIDAL SOURCES OF THYROID HORMONE					
Endogenous (struma ovarii, ovarian teratoma, metastatic follicular carcinoma)	Decreased	Increased	None	Decreased	Low thyroglobulin since endogenous thyroid hormone production suppressed
Exogenous (drugs)	Decreased	Increased (T_4 would be decreased if taking T_3)	None	Decreased	
EXCESSIVE THYROID STIMULATION					
Pituitary Thyrotropinoma	Increased or inappropriately normal	Increased	None	Increased	Pituitary mass; possible PRL or GH excess
Pituitary Thyroid Hormone Receptor Resistance	Increased or normal	Increased	None	Increased	Abnormal THRB gene analysis
Increased hCG (e.g. pregnancy)	Decreased	Increased	None	Test is contraindicated in pregnancy	

Signs and Symptoms of HYPERthyroidism

THYROIDISM
Tremor
Heart rate up
Yawning (fatigue due to insomnia)
Restlessness
Oligomenorrhea/amenorrhea
Intolerance to heat
Diarrhea
Irritability
Sweating
Muscle wasting/weight loss

Common Etiologies

Thyrotoxicosis	Hypothyroidism
Graves' Disease	Hashimoto's
Toxic Nodular Goitre	Congenital
Toxic Nodule	Iatrogenic (thionamides, radioactive iodine, or surgery)
Hyperthyroid phase of thyroiditis	Hypothyroid phase of thyroiditis

Clinical Features

Table 17. Clinical Features of Thyrotoxicosis

General	**Fatigue, heat intolerance, irritability, fine tremor**
CVS	Tachycardia, atrial fibrillation, palpitations Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation
GI	Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)
Neurology	Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asian individuals)
GU	Oligomenorrhea, amenorrhea, decreased fertility
Dermatology	Fine hair, moist and warm skin, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema, pruritus Graves' disease: clubbing (acropachy), pretibial myxedema (rare)
MSK	Decreased bone mass, proximal muscle weakness
Hematology	Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)
Eye	Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjunctival injection NOTE: Lid lag is a reflection of a hyperadrenergic state and can be present in any form of thyrotoxicosis

Treatment
- β-blockers for control of adrenergic symptoms
- antithyroidals (thionamides): methimazole (MMI) recommended, or propylthiouracil (PTU)
  - to prepare patients with endogenous hyperthyroidism for surgery, for patients with Graves' disease, and for patients with toxic nodules who do not wish to have definitive treatment with radioactive iodine or surgery
- radioactive iodine thyroid ablation for Graves' disease and toxic nodules/adenoma
- surgery in the form of hemi, subtotal, or complete thyroidectomy for toxic nodules
- surgery in the form of total thyroidectomy for Graves' disease

Graves' Disease

Definition
- an autoimmune disorder characterized by autoantibodies that stimulate the TSH receptor leading to hyperthyroidism

Epidemiology
- most common cause of hyperthyroidism
- occurs at any age with peak in 3rd and 4th decade
- F:M=7:1, 1.5-2% of women in the United States
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA-B8 and DR3
- may be associated with other autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathophysiology
- autoimmune disorder due to breakdown in thyroid tolerance likely due to a combination of factors including autoreactive B lymphocytes and an imbalance favouring a TH2 vs. TH1 immune response
- B lymphocytes produce TSI that binds and stimulates the TSH receptor, and thus, the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, viral or bacterial infections, and glucocorticoid withdrawal
- ophthalmopathy (thyroid associated orbitopathy) is a result of increased connective and extraocular muscle tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit; this leads to fluid accumulation and forward displacement of the eyeball
- dermopathy (pretibial or localized myxedema) may be related to cutaneous glycosaminoglycan deposition

Clinical Features
- signs and symptoms of thyrotoxicosis
- diffuse goitre ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity (plus signs of hyperthyroidism: lid retraction, characteristic stare)
- dermopathy (rare): pretibial myxedema (thickening of dermis that manifests as non-pitting edema)
- acropachy: clubbing and thickening of distal phalanges

Investigations
- low TSH
- increased free T4 (and/or increased T3)
- positive for TRAb (the currently available third-generation TRAb tests have sensitivity and specificity over 98%, allowing their use for determining the etiology of hyperthyroidism)
- increased RAIU
- homogeneous diffuse uptake on thyroid scan

Graves' Ophthalmopathy

NO SPECS (in the usual order of changes)
No signs
Only signs: lid lag, lid retraction
Soft tissue: periorbital puffiness, conjunctival injection, chemosis
Proptosis/exophthalmos
Extraocular (diplopia)
Corneal abrasions (unable to close eyes)
Sight loss

Other Medications Used in the Treatment of Graves'

Glucocorticoids have been useful in the treatment of severe Graves' hyperthyroidism and thyroid storm, by inhibiting the conversion of peripheral T_4 to T_3

Lithium can also be used to treat Graves' hyperthyroidism. It acts by blocking thyroid hormone release, but its toxicity has limited its use in practice

Caution with Thionamides
These drugs are highly effective inhibitors of thyroid hormone synthesis, inducing permanent remission in 20-30% of patients with Graves' disease. They are most often employed to achieve a euthyroid state before definitive treatment. Adverse effects include teratogenicity, agranulocytosis, hepatotoxicity, and ANCA-positive vasculitis

Treatment

- thionamides (antithyroid medications): MMI or PTU
  - PTU and MMI inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines
  - PTU also inhibits peripheral deiodination of T4 to T3
  - treat for approximately 12-18 mo aiming for a normal TSH and TRAb prior to consideration of treatment discontinuation
  - small goitre, mild hyperthyroidism, and low TRAb titres are good predictors for long-term remission with medical therapy
  - remission (normal thyroid indices one yr after discontinuation of PTU or MMI) rates range between 20-50% following 12-18 mo of antithyroid medication
  - major side effects: hepatotoxicity (cholestasis, hepatitis), agranulocytosis, vasculitis
  - minor side effects: mild rash, pruritus
  - MMI is preferred to PTU due to longer duration of action (once daily dosing for most), more rapid resolution of hyperthyroidism, and lower incidence of side effects
  - in pregnancy: use PTU during the first 16 wk of pregnancy and MMI after. MMI is contraindicated in the first trimester due to risk of aplasia cutis; MMI is preferred in the second and third trimester due to the potential risk of hepatotoxicity with PTU in the second and third trimesters
- symptomatic treatment with β-blockers
- thyroid ablation with radioactive I-131 if PTU or MMI trial does not produce disease remission or patient prefers definitive treatment with RAI
  - high incidence of hypothyroidism after I-131 requiring lifelong thyroid hormone replacement
  - contraindicated in pregnancy
  - may worsen ophthalmopathy; concurrent treatment with prednisone if high risk for or if ophthalmopathy present
- total or near total thyroidectomy
  - indicated for large goitres, suspicious nodule for cancer, if patient is intolerant to thionamides and declines/is not a candidate for RAI ablation, women who wish to conceive in the near future warranting rapid control of hyperthyroidism, uncontrolled hyperthyroidism not responding to anti-thyroid drugs in pregnancy (surgery safest in second trimester), patient preference
  - risks: permanent hypothyroidism, hypoparathyroidism, and vocal cord palsy due to potential laryngeal nerve damage
- ophthalmopathy/orbitopathy
  - smoking cessation is important
  - prevent drying of eyes and ulceration of cornea by using artificial tears during the day and lubricants at night
  - high dose prednisone or IV methylprednisolone in severe cases
  - high dose glucocorticoids (preferably IV) as well as potential orbital decompression surgery for sight-threatening orbitopathy
  - orbital radiation, surgical decompression

Prognosis

- course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
- total and subtotal thyroidectomy are rapid cures with low-risk of recurrence (2% and 10%, respectively)
- radioactive iodine is less invasive than surgery, but also results in permanent hypothyroidism and requires precautions in contacts several days after treatment
- medical therapy with thionamides is not invasive, but has high recurrence rate at ~50%
- lifetime follow-up needed

Subacute Thyroiditis (Thyrotoxic Phase)

- there are two main types: painful (de Quervain's) and painless (silent)

Table 18. Painful vs. Painless Subacute Thyroiditis

	Painful Thyroiditis (de Quervain's, granulomatous)	Painless Thyroiditis (silent, autoimmune)
Pathophysiology	Presumed to be caused by viral infection or postviral inflammatory process Strongly associated with HLA-D35 Thyroid inflammation damages thyroid follicles, resulting in release of large amounts of T4 and T3 until stores are exhausted State of hypothyroidism often persists until thyroid can generate sufficient thyroid hormones	Considered variant of Hashimoto's thyroiditis Associated with HLA-DR3 Postpartum subtype occurs following pregnancy Also caused by inflammatory damage leading to unregulated release of T_4 and T_3 into circulation
Clinical Features	Painful swelling of the thyroid (may radiate to jaw and ears), transient vocal cord paresis, malaise, fatigue, myalgia, fever Often preceded by URTI Painful condition lasts for a week to few months Signs of hyperthyroidism during hyperthyroid phase (palpitations, tachycardia, stare)	Thyroid enlargement without discomfort in association with the typical thyroid function test abnormalities consisting of hyperthyroidism, hypothyroidism, and recovery Signs of hyperthyroidism during hyperthyroid phase (palpitations, tachycardia, stare) Affects women more than men
Laboratory Investigations	Initial elevated T_4 and T_3 Near absent RAIU ESR and CRP often elevated	Initial elevated T_4 and T_3 Near absent RAIU
Treatment	NSAID/prednisone for pain β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms If symptomatically hypothyroid, may treat short-term with thyroxine	β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms If symptomatically hypothyroid, may treat short-term with thyroxine
Prognosis	Complete spontaneous recovery to normal thyroid function in 90% of patients 10% of patients may become hypothyroid and require permanent replacement	10% of patients may become permanently hypothyroid At risk of recurrent episodes of thyroiditis

Toxic Adenoma/Toxic Multinodular Goitre

Etiology and Pathophysiology

- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting T4 and T3
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre (Plummer's disease))
- more common in elderly people as opposed to Graves' disease, which is more common in younger individuals

Clinical Features

- may have multinodular goitre
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- local neck compression symptoms such as dysphagia, dysphonia, or dyspnea may be present with large goitres

Investigations

- low TSH, high free T4 and free T3
- thyroid scan with increased RAIU in nodule(s) and suppression of the remainder of the gland

Treatment

- use high dose radioactive iodine (I-131) to ablate hyperfunctioning nodules
- β-blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as first-line treatment
- initiate therapy with MMI or PTU to attain euthyroid state in individuals who do not wish to have definitive treatment of their disease, in preparation for thyroidectomy, or prior to RAI in patients at risk for complications due to exacerbation of hyperthyroidism following RAI such as the elderly with cardiovascular disease

Thyrotoxic Crisis/Thyroid Storm

Definition

- medical emergency – acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism
- rare, but serious with mortality rate between 10-30%

Etiology and Pathophysiology

- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

Differential Diagnosis
- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

Clinical Features
- hyperthyroidism
- extreme hyperthermia (≥40°C), tachycardia, vomiting, diarrhea, hepatic failure with jaundice, atrial fibrillation, CHF
- CNS manifestations including agitation, delirium, psychosis, lethargy, seizures, coma

Laboratory Investigations
- increased free T4 and T3, undetectable TSH
- ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

General Measures
- fluids, electrolytes, and vasopressor agents should be used as indicated
- a cooling blanket and acetaminophen can be used to treat the pyrexia
- propranolol or other β-blockers can additionally be used
  - use with caution in patients with decompensated heart failure as they may worsen condition
  - propranolol is frequently used because it decreases peripheral conversion of T4 to T3

Specific Measures
- PTU is the anti-thyroid drug of choice and is used in high doses (200 mg q4 h)
- give iodide, which acutely inhibits the release of thyroid hormone, 1 h after the first dose of PTU is given
  - sodium iodide 1 g IV drip over 12 h q12 h
    OR
  - Lugol's solution 10 drops q8 h
    OR
  - potassium iodide (SSKI) 5 drops q6 h
- hydrocortisone 100 mg IV q8 h or dexamethasone 2-4 mg IV q6 h for the first 24-48 h; inhibits peripheral conversion of T4 to T3

Hypothyroidism

Definition
- clinical syndrome caused by insufficient thyroid hormone production

Epidemiology
- 2-3% of general population
- F:M=10:1
- 10-20% of women >50 have subclinical hypothyroidism (normal T4, TSH mildly elevated)
- iodine deficiency is the most common cause worldwide, but not in North America

Etiology and Pathophysiology
- primary hypothyroidism (90%)
  - inadequate thyroid hormone production due to an intrinsic thyroid defect
  - iatrogenic: post-ablative (I-131 or surgical thyroidectomy)
  - autoimmune: Hashimoto's thyroiditis
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4000 births)
  - neoplasia
- secondary hypothyroidism: pituitary hypothyroidism
- insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
- decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

Table 19. Interpretation of Serum TSH and Free T_4 in Hypothyroidism

	Serum TSH	Free T_4
Overt Primary Hypothyroidism	Increased	Decreased
Subclinical Primary Hypothyroidism	Increased	Normal
Secondary Hypothyroidism	Decreased or not appropriately elevated	Decreased

Factors Affecting Gastrointestinal Absorption of Levothyroxine: A Review
Clin Ther 2017;39(2):378-403
- GI disorders such as celiac disease, atrophic gastritis, lactose intolerance, H. pylori infection may impede levothyroxine absorption.
- Drugs decreasing stomach acidity have been shown to significantly reduce exogenous thyroid hormone absorption from the GI tract. These include proton-pump inhibitors, H2 receptor antagonists, calcium carbonate, sucralfate, and aluminum hydroxide.
- Iron citrate is shown to reduce intestinal absorption of levothyroxine.
- Food, especially soybeans and coffee, have been shown to reduce absorption of levothyroxine significantly.
- Roughly 80% of levothyroxine is absorbed within 3 h after administration of the drug. Thus, patients should be educated to take levothyroxine on empty stomach at least 1 h prior to eating breakfast.

Clinical Features

Table 20. Clinical Features of Hypothyroidism

General	Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia
CVS	Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart
Respiratory	Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia
GI	Weight gain despite poor appetite, constipation
Neurology	Paresthesia, slow speech, muscle cramps, delayed deep tendon reflex relaxation ("hung reflexes"), carpal tunnel syndrome, asymptomatic elevated CK, seizures
GU	Menorrhagia, amenorrhea, impotence, pre-menopausal abnormal vaginal bleeding
Dermatology	Facial puffiness, periorbital edema, cool and pale, dry and rough skin, dry and coarse hair, eyebrows thinned (lateral 1/3), discolouration (carotenemia)
Hematology	Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto's thyroiditis

Treatment
- L-thyroxine (dose range: 0.05-0.2 mg PO once daily, up to 1.6 µg/kg/d)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; adjust dose until TSH returns to normal reference range
- once maintenance dose achieved, follow up TSH with patient annually
- secondary/tertiary hypothyroidism: monitor via measurement of free T4 (TSH is unreliable in this setting)

CONGENITAL HYPOTHYROIDISM
- see Pediatrics, P35

Hashimoto's Thyroiditis

Definition
- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a small, rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from onset
- risk factor for rare primary thyroid lymphoma

Etiology and Pathophysiology
- defect in a T-suppressor clone leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na+/I– symporter

Risk Factors
- F:M=7:1
- genetic susceptibility: increased frequency in patients with Down's syndrome, Turner's syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake

Investigations
- high TSH, low T4 (not necessary to measure T3 as it will be low as well)
- presence of TPOAb and TgAb in serum

Treatment
- if hypothyroid, replace with L-thyroxine (analog of T4)

Myxedema Coma

Definition
- medical emergency – severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events
- rare; high level of mortality (up to 40%, despite therapy)

Subclinical Hypothyroidism: A Review
JAMA 2019;322:153-160
Background: Up to 10% of the adult population experiences subclinical hypothyroidism, defined as elevated TSH (>4.4 mU/L) with normal levels of free T4. The degree of abnormality that warrants management is controversial.
Observations: Subclinical hypothyroidism is most often caused by autoimmune thyroiditis. It may be associated with increased risk of CHF and CAD events. Further, a substantial portion of patients with subclinical hypothyroidism progress to overt hypothyroidism. Evidence from large RCTs to support levothyroxine therapy in these patients is lacking. The rationale for treatment is therefore based on levothyroxine's potential to prevent cardiovascular events and progression to overt hypothyroidism.
Recommendations: Most individuals with subclinical hypothyroidism can be observed without treatment. Candidates for levothyroxine therapy include those with serum TSH levels >10 mU/L and young and middle-aged patients with symptoms of mild hypothyroidism.

Signs and Symptoms of HYPOthyroidism

HIS FIRM CAP
Hypoventilation
Intolerance to cold
Slow HR
Fatigue
Impotence
Renal impairment
Menorrhagia/amenorrhea
Constipation
Anemia
Paresthesia

Clinical Features
- decreased mental status and hypothermia are hallmark symptoms
- hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized non-pitting edema often present

Investigations
- decreased T4, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment
- aggressive and immediate treatment required
- ABC's: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8 h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV once daily until oral therapy tolerated; also consider T3 therapy
- supportive measures: mechanical ventilation, vasopressors, passive rewarming, IV dextrose, fluids if necessary (risk of overload)
- monitor for arrhythmia

Non-Thyroidal Illness (Sick Euthyroid Syndrome)

Definition
- changes in the regulation of the hypothalamic-pituitary-thyroid axis, and thyroid hormone metabolism and transport among patients with severe illness, trauma, surgery, or starvation
- not due to intrinsic thyroid, pituitary, or hypothalamic disease
- initially low free T3 may be followed by low TSH and, if severe illness, low free T4
- with recovery of illness, TSH may become transiently high

Pathophysiology
- abnormalities include alterations in:
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
- may be protective during illness by reducing tissue catabolism

Labs
- initially decreased free T3 followed by decreased TSH and finally decreased free T4
- with recovery of illness, TSH may become elevated

Treatment
- treat the underlying disease; thyroid hormone replacement has not shown to be beneficial
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

Non-Toxic Goitre
Definition
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

Pathophysiology
- the appearance of a goitre is more likely to present during adolescence, pregnancy, and lactation due to increased thyroid hormone requirements
- early stages: goitre is usually diffuse
- later stages: multinodular non-toxic goitre with nodule, cyst formation, and areas of ischemia, hemorrhage, and fibrosis

Etiology
- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

Treatment
- remove goitrogens
- radioiodine therapy (very high doses required given low iodine uptake, used as last resort in very highly selected cases where the goiter is causing symptoms and surgery is not feasible)
- suppression with L-thyroxine (rarely done)
- surgery may be necessary if severe compressive symptoms develop (rare); patients are often asymptomatic

Complications
- compression of neck structures causing stridor, dysphagia, pain, and hoarseness of voice
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Thyroid Nodules

Definition
- discrete lesion that can be distinguished sonographically from the rest of the thyroid parenchyma
- 19-67% prevalence based on incidentally found nodules on U/S

Etiology
- benign tumours (e.g. follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

Investigations
- approach to thyroid biopsy depending on U/S characteristics of the nodule
- benign or very small nodules suspicious for thyroid cancer do not require ongoing surveillance
- small nodules suspicious for thyroid cancer require up to five years of surveillance
- larger nodules suspicious for thyroid cancer require biopsy

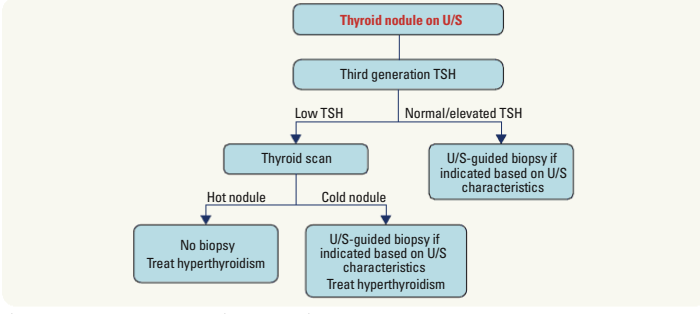


Figure 12. Approach to the evaluation of a thyroid nodule
Adapted from Dr. J Goguen, University of Toronto, MMMD 2013

Thyroid Malignancies

- see Otolaryngology, OT38

Adrenal Cortex

Adrenocorticotropic Hormone
- a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400 h; trough: 1800-2400 h)
- secretion regulated by CRH and AVP
- stimulates growth of adrenal cortex and release of glucocorticoids, adrenal androgens and, to a very limited extent, mineralocorticoids
- ACTH can directly bind to MSH receptors on melanocytes, enhancing melanogenesis

Adrenocortical Hormones

Aldosterone
- a mineralocorticoid which regulates ECFV through Na^+ (and Cl^-) retention and K^+ (and H^+) excretion (stimulates distal tubule Na^+/K^+-ATPase)
- regulated by the RAAS and hyperkalemia
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone ↑ volume expansion) and short loop (angiotensin II ↑ peripheral vasoconstriction)

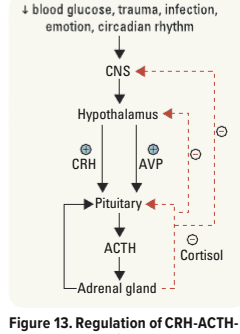
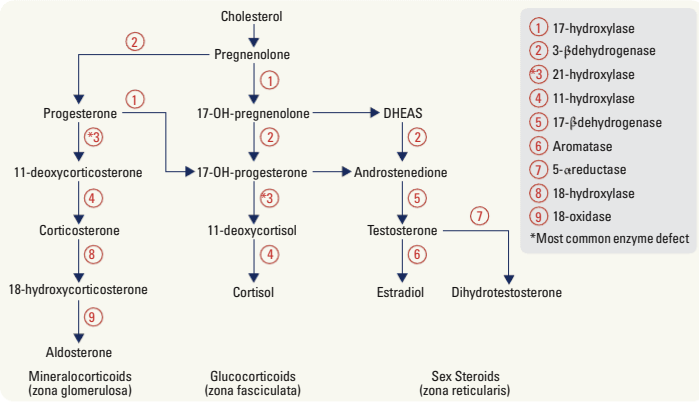


Figure 13. Regulation of CRH-ACTH-adrenal gland axis



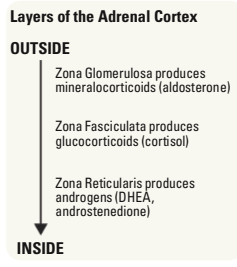


Figure 14. Pathways of major steroid synthesis in the adrenal gland and their enzymes

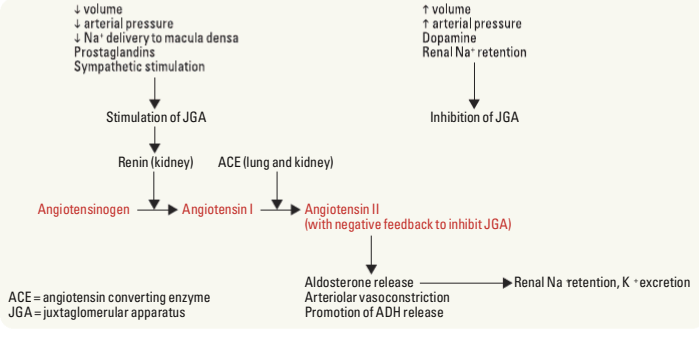


Figure 15. Renin-angiotensin-aldosterone axis (see Nephrology, NP5)

Cortisol

- a glucocorticoid regulated by the HPA axis
- involved in metabolism regulation
- supports blood pressure and vasomotor tone
- also involved in behavioural regulation and immunosuppression

Table 21. Physiological Effects of Glucocorticoids

Stimulatory Effects	Inhibitory Effects
Stimulate hepatic glucose production (gluconeogenesis)	Inhibit bone formation; stimulate bone resorption
Increase insulin resistance in peripheral tissues	Inhibit fibroblasts, causing collagen and connective tissue loss
Increase protein catabolism	Suppress inflammation; impair cell-mediated immunity
Stimulate leukocytosis and lymphopenia	Inhibit growth hormone axis*
Increase cardiac output, vascular tone, Na^+ retention	Inhibit reproductive axis*
Increase PTH release, urine calcium excretion	Inhibit vitamin D_3 and inhibit calcium uptake

*Typically only occurs with cortisol excess

Androgens

- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are: DHEA, androstenedione, and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases with age

Adrenocortical Functional Workup

Stimulation Test
- purpose: diagnose hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

Tests of Glucocorticoid Reserve
- Cosyntropin (ACTH analogue) Stimulation Test
  - administer 250 µg cosyntropin IV/IM, and measure plasma cortisol levels before and 30 and 60 min after administration
  - physiologic response: stimulated plasma cortisol of >500 nmol/L (>18 µg/dL) at 30 or 60 min
    - physiologic response rate threshold may be lower with newer assays and should be confirmed with local lab
  - inappropriate response: inability to stimulate increased plasma cortisol; peak cortisol levels below 500 nmol/L (18 µg/dL) at 30 or 60 min

Suppression Tests
- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

1. Tests of Pituitary-Adrenal Suppressibility
- DXM suppression test
- principle: DXM suppresses pituitary ACTH, plasma cortisol should be lowered if HPA axis is normal
- screening test: low-dose overnight DXM suppression test
    - oral administration of 1 mg DXM between 11 pm and midnight, then measure plasma cortisol levels the following day between 8 am and 9 am
    - physiologic response: plasma cortisol <50 nmol (<1.8 µg/dL)
    - inappropriate response: failure to suppress plasma cortisol
    - false positive results due to obesity, depression, alcoholism, pregnancy, medications or oral contraceptive pills inducing the metabolism of DXM
  - testing of excess cortisol production
    - elevated 24 h urine free cortisol (shows overproduction of cortisol)
    - midnight salivary cortisol (if available) shows lack of diurnal variation
      - inappropriately remains high, >145 ng/dL (4 nmol/L) (normally will be low at midnight)

2. Tests of Mineralocorticoid Suppressibility
- multiple medications can interfere with the interpretation of screening and confirmatory tests for PA and these may need to be held prior to testing
- positive screen for PA is elevated aldosterone:renin ratio in the presence of high aldosterone
  - there is variability in the interpretation of aldosterone:renin ratio depending on the assays used
- confirmation of PA requires lack of aldosterone suppression: with expansion of ECFV, plasma aldosterone should be lowered
- ECFV Expansion with NS
  - IV infusion of 500 mL/h of NS for 4 h, then measure plasma aldosterone levels
  - plasma aldosterone >277 pmol/L is consistent with PA, <140 pmol/L is normal
  - inappropriate response: failure to suppress plasma aldosterone

Mineralocorticoid Excess Syndromes

Definition
- PA: excess aldosterone production (intra-adrenal cause) (previously called hyperaldosteronism)
- SA: aldosterone production in response to excess RAAS (extra-adrenal cause)

Etiology
- aldosterone-producing adrenal adenoma (Conn's syndrome)
- bilateral or idiopathic adrenal hyperplasia
- glucocorticoid-remediable aldosteronism
- aldosterone-producing adrenocortical carcinoma
- unilateral adrenal hyperplasia
- ectopic aldosterone-producing tumours
- familial hyperaldosteronism (FH) types I-IV

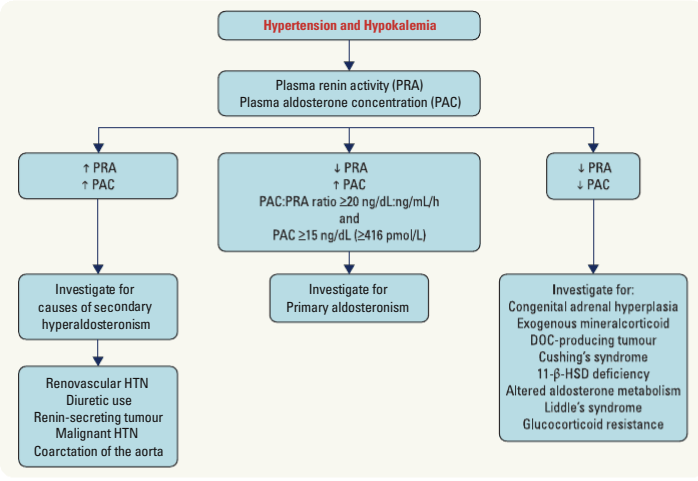


Figure 16. Approach to mineralocorticoid excess syndromes

Clinical Features

- HTN
- hypokalemia (± mild hypernatremia), metabolic alkalosis
- normal K^+, hyponatremia in secondary hyperaldosteronism (low effective circulating volume leads to ADH release)
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, and MI
- elevated risk of metabolic syndrome and T2DM
- fatigue, weakness, paresthesia, headache; severe cases present with tetany, intermittent paralysis (only if $K^+ < 2.5$ mEq/L)

Diagnosis

- investigate plasma aldosterone:renin ratio in patients with HTN and hypokalemia, drug resistant HTN, HTN and a first degree relative with PA, HTN and a family history of stoke in a first degree relative ≤40 yr, HTN and adrenal incidentaloma
- confirmatory testing for PA: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECF volume expansion), adrenal vein sampling may be required to determine whether there is lateralization of aldosterone excess
- imaging: CT adrenal glands

Table 22. Diagnostic Tests in Hyperaldosteronism

Test	Primary Hyperaldosteronism	Secondary Hyperaldosteronism
Plasma Aldosterone to Renin Ratio (PAC/PRA)	Elevated (↑ aldosterone, ↓ renin)	Normal (↑ aldosterone, ↑ renin)
Salt Loading Test (confirmatory test)		
A) Oral Salt Test	↑ 24 hour urine aldosterone	Not performed
B) IV Saline Test	Plasma aldosterone concentration >277 pmol/L (140-277 indeterminant range)	Not performed

Treatment

- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause

Cushing's Syndrome

Definition
- metabolic disorder caused by chronic glucocorticoid excess

Etiology
- ACTH-dependent (85%) – bilateral adrenal hyperplasia and cortisol hypersecretion due to:
  - ACTH-secreting pituitary adenoma (Cushing's disease; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, pancreatic islet cell, pheochromocytoma, or medullary thyroid tumour)
- ACTH-independent (15%)
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia
- iatrogenic Cushing's syndrome is likely more common than endogenous cortisol excess; it is ACTH-independent

Clinical Features
- symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism, and acne (ACTH dependent)
- signs: central obesity, round face ("moon face"), supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, HTN, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism (if ACTH-dependent)

Diagnosis
- rule out excessive glucocorticoid exposure leading to iatrogenic Cushing's syndrome by conducting a thorough drug history before conducting biochemical testing
- perform at least one of: 1) 24 h urine free cortisol (≥2 tests), 2) low dose DXM suppression test, or 3) late night salivary cortisol (≥2 tests)
- consider reasons for a false positive (e.g. pregnancy, depression, alcoholism, morbid obesity, poorly controlled DM, glucocorticoid resistance, physical stress, malnutrition, anorexia nervosa, intense chronic exercise, hypothalamic amenorrhea, on oral contraceptive pills)
- confirm with one of the remaining tests

Treatment
- adrenal
  - adenoma: unilateral adrenalectomy (curative) with glucocorticoid supplementation postoperatively, tapering slowly until HPA axis has recovered
  - carcinoma: adrenalectomy in patients with disease localized to the adrenal, adjunctive mitotane for individuals with high-risk for current disease. Mitotane ± chemotherapy for patients with metastatic disease
  - medical treatment: ketoconazole to reduce cortisol, mitotane can be used – typically reserved for patients with malignant disease
- pituitary
  - transsphenoidal resection, with glucocorticoid supplementation postoperatively
  - if surgery delayed, contraindicated, or unsuccessful, consider medical management e.g. ketoconazole, mitotane, pasireotide, or cabergoline
- ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis) - surgical resection, if possible; chemotherapy/radiation for primary tumour
  - medical treatment with mitotane or ketoconazole to reduce cortisol synthesis. Often required when surgery is delayed, contraindicated, or unsuccessful
- treat comorbidities associated with hypercortisolism

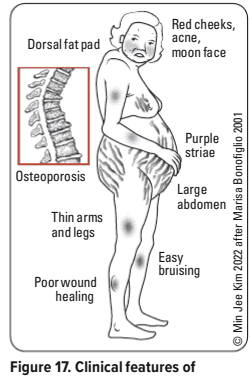


Figure 17. Clinical features of Cushing's syndrome

Congenital Adrenal Hyperplasia

- see Pediatrics, P37

Hyperandrogenism

Definition
- state of having excessive secretion of androgens (DHEA, DHEA-sulfate, testosterone)

Etiology and Pathophysiology

Table 23. Etiology of Hyperandrogenism

Medications Androgen-Mediated	Anabolic steroids, ACTH, androgens, progestational agents
Ovarian	PCOS Ovarian hyperthecosis Theca cell tumours Pregnancy: placental sulfatase/aromatase deficiency
Adrenal	Congenital adrenal hyperplasia (CAH, late-onset CAH) Tumours (adenoma, carcinoma)
Pituitary	Cushing's disease – high ACTH Hyperprolactinemia

Clinical Features

Females
- hirsutism
  - male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  - Ferriman-Gallwey scoring system is used to quantify severity of hirsutism (score of >8 is abnormal for white/black women, ≥9 abnormal for Mediterranean/Hispanic/Middle-Eastern women, ≥2 for Asian women)
    - scores should be interpreted in the context of the specific patient and acknowledge limitations such as the use of cosmetic hair removal
  - scores between 8-15 are mild, 16-25 moderate, and >25 severe hirsutism
- alopecia (male pattern hair loss)
- acne
- virilization
  - frontal balding, clitoromegaly, increased muscle mass, deepening of the voice
- amenorrhea, ↓ breast size, infertility, anabolic appearance

Conditions that do Not Represent True Hirsutism

Androgen-independent hair (e.g. lanugo hair)

Drug-induced hypertrichosis (e.g. phenytoin, diazoxide, cyclosporine, minoxidil)

Topical steroid use

Males
- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in testicular size, testicular testosterone production, and spermatogenesis

Investigations
- testosterone, DHEA-S as a measure of adrenal androgen production
- LH/FSH (commonly in PCOS >2.5)
- 17-OH progesterone, elevated in CAH due to 21-OH deficiency; check on day 3 of menstrual cycle with a progesterone level
- for virilization: CT/MRI of adrenals and ovaries (identify tumours)
- if PCOS, check blood glucose and lipids

Treatment
- discontinue causative medications (e.g. oral DHEA, valproate, danazol)
- antiandrogens, e.g. spironolactone
- oral contraceptives (increase sex hormone binding globulin, which binds androgens>estrogens; reduces ovarian production of androgens)
- surgical resection of tumour
- glucocorticoid ± mineralocorticoid if CAH confirmed
- treat specific causative disorders, e.g. tumours, Cushing's, etc.
- cosmetic therapy (laser, electrolysis)

Adrenocortical Insufficiency

Definition

- state of inadequate cortisol and/or aldosterone production by the adrenal glands

Etiology

PRIMARY ADRENOCORTICAL INSUFFICIENCY

Table 24. Etiology of Primary Adrenocortical Insufficiency

Autoimmune (70-90%)	Isolated adrenal insufficiency (Addison's Disease) Polyglandular autoimmune syndromes types I and II Antibodies often directed against adrenal enzymes and 3 cortical zones
Infections	Tuberculosis (7-20%) (most common in developing world) Fungal: histoplasmosis, paracoccidioidomycosis HIV, CMV Syphilis African trypanosomiasis
Infiltrative	Metastatic cancer (lung>stomach>esophagus>colon>breast); lymphoma Sarcoidosis, amyloidosis, hemochromatosis
Vascular	Bilateral adrenal hemorrhage (risk increased by heparin and warfarin) Sepsis (meningococcal, Pseudomonas) Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children Thrombosis, embolism, adrenal infarction
Drugs	Inhibit cortisol: ketoconazole, etomidate, megestrol acetate Increase cortisol metabolism: rifampin, phenytoin, barbiturates
Others	Adrenoleukodystrophy and adrenomyeloneuropathy Congenital adrenal hypoplasia (impaired steroidogenesis) Familial glucocorticoid deficiency or resistance Defective cholesterol metabolism

SECONDARY ADRENOCORTICAL INSUFFICIENCY

- inadequate pituitary ACTH secretion
- multiple etiologies (see *Hypopituitarism, E23*), including withdrawal of exogenous steroid

Clinical Features

Table 25. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)

	Primary AI (Addison's or Acute AI)	Secondary AI
Skin and Mucosa	Dark (palmar crease, extensor surface)	Pale
Potassium	High	Normal
Sodium	Normal or low	Normal or Low
Metabolic Acidosis	Present	Absent
Associated Diseases	Primary hypothyroidism, T1DM, vitiligo	Central hypogonadism or hypothyroidism, growth hormone deficiency, DI
Associated Symptoms	Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia GI: N/V, abdominal pain, diarrhea	Weakness, fatigue, weight loss, hypotension, postural dizziness, myalgia, arthralgia, headaches, visual abnormalities
Diagnostic Test	Cosyntropin Stimulation Test High morning plasma ACTH High renin	Insulin tolerance test Cosyntropin Stimulation Test Low or inappropriately normal morning plasma ACTH

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

Treatment

- acute adrenal crisis – can be life-threatening
  - IV NS 1 L within the first hour followed by continuous IV NS guided by patient requirements; add D5W if hypoglycemic
  - hydrocortisone 100 mg IV stat followed by 50 mg IV q6 h
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-25 mg PO or cortisone acetate 20-35 mg PO total daily dose in 2-3 divided doses, highest dose in the morning
  - prednisolone 3-5 mg once daily or 3-5 mg BID can be used as an alternative to hydrocortisone, especially in patients with reduced compliance
  - Florinef™ (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO once daily in primary adrenal insufficiency
  - stress dosing
    - increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
    - major stress (e.g. surgery, trauma) requires 150-300 mg hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection

Adrenal Medulla

Catecholamine Metabolism

- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine)
- broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine

ABC of Adrenaline

Adrenaline activates
β-receptors, increasing
Cyclic AMP

Pheochromocytoma/Paraganglioma

Definition

- paragangliomas are rare neuroendocrine tumours that arise from the extra-adrenal autonomic paraganglia (small organs comprised of neuroendocrine cells that secrete catecholamines)
- pheochromocytomas are catecholamine-secreting tumours derived from chromaffin cells of the adrenal gland

Epidemiology

- most commonly a single tumour of adrenal medulla
- rare cause of HTN (<0.2% of all hypertensives)

Etiology and Pathophysiology

- pheochromocytomas and paragangliomas have the greatest genetic inheritance among neuroendocrine tumours
- 30-40% cases are linked to germline mutations, including mutations in the RET, VHL, SDHx, NF1, and SDHAF2 genes
- pheochromocytomas and paragangliomas are divided into clusters: cluster 1 - Pseudohypoxia subtype (FH, VHL/EPAS1-related), cluster 2 - Kinase signaling group (HRAS), cluster 3 - WNT signaling group (CSDE1, UBTF-MAML3 fusion)
- most cases are sporadic; 40% of affected patients have an associated familial disorder. In these patients, the tumours are more likely bilateral adrenal pheochromocytomas/paraganglioma
- hereditary forms present earlier than sporadic cases
- several familial disorders are associated with adrenal pheochromocytoma, all have autosomal dominant inheritance, e.g. multiple endocrine neoplasia type 2 (MEN2) - 50% frequency, von Hippel-Lindau (VHL) syndrome - 10-20% frequency, and less commonly, neurofibromatosis type 1 (NF1) - 0.1-5.7% frequency
- some tumours, via an unknown mechanism, are able to synthesize and release excessive catecholamines

Clinical Features

- 50% suffer from paroxysmal HTN; others have sustained HTN
- classic triad (not found in most patients): episodic "pounding" headache, palpitations/tachycardia, diaphoresis
- other symptoms: tremor, anxiety, chest or abdominal pain, N/V, visual blurring, weight loss, polyuria, polydipsia
- other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
- symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods – such as aged/strong cheese and cured meats)

Investigations

- urine metanephrines
  - increased catecholamine metabolites (metanephrines) and catecholamines
  - plasma metanephrines, if available (most sensitive)
    - cut-off values will depend on assay used
- CT abdomen
  - if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

Treatment

- surgical excision of tumour (curative) with careful pre- and postoperative ICU monitoring
- adequate preoperative preparation
  - α-blockade for BP control: doxazosin or phenoxybenzamine (these are the most frequently used alpha blockers) (10-21 d preoperative), IV phentolamine (perioperative if required)
  - β-blockade if needed for HR control once α blocked for a few days
  - metyrosine (catecholamine synthesis inhibitor) + alpha blocker
  - volume restoration with vigorous salt-loading and fluids
- monitor for hypoglycemia postoperatively
- rescreen urine 1-3 mo postoperatively
- all patients are currently offered genetic testing - probability of germline disease increases with young age, multifocal disease, in the setting of paraganglioma

Disorders of Multiple Endocrine Glands

Multiple Endocrine Neoplasia

Definition

- neoplastic syndromes involving multiple endocrine glands
- tumours of neuroectodermal origin
- autosomal dominant inheritance with variable penetrance

MEN 1 Affects the 3 Ps
Pituitary
Parathyroid
Pancreas

Table 26. MEN Classification

Type	Tissues Involved	Clinical Manifestations
MEN 1 (chromosome 11)		
3 Ps (Pituitary, parathyroid and pancreas)	Pituitary (30-40%) Anterior pituitary adenoma	Headache, visual field defects, most commonly secrete PRL (prolactinomas are the most common pituitary functional tumour in MEN 1 leading to galactorrhea, erectile dysfunction, decreased libido, amenorrhea), GH (acromegaly). GH+PRL, ACTH (Cushing's), non-functional less common
	Parathyroid (≥95%) Primary hyperparathyroidism from hyperplasia or adenomas	Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcemia
	Entero-pancreatic endocrine (30-80%) Pancreatic islet cell tumours Gastrinoma Insulinomas Vasoactive intestinal peptide (VIP)-omas Glucagonoma Carcinoid syndrome Non-functional pancreatic neuroendocrine tumours	Epigastric pain (peptic ulcers and esophagitis) Hypoglycemia Secretory diarrhea Rash (necrolytic migratory erythema), anorexia, anemia, diarrhea, glossitis Flushing, diarrhea, bronchospasm
	Adrenal tumours (~40%)	
MEN 2 (chromosome 10)		
1. MEN 2A (Sipple's Syndrome)	Thyroid (~90%) Medullary thyroid cancer (MTC)	Physical signs are variable and often subtle
	Adrenal medulla (40-50%) Pheochromocytoma (40-50%)	Neck mass or thyroid nodule; non-tender, anterior lymph nodes HTN, palpitations, headache, sweating
	Parathyroid (20-30%) 1° parathyroid hyperplasia	Symptoms of hypercalcemia
	Skin Cutaneous lichen amyloidosis	Scaly skin rash
2. Familial MTC (a variant of MEN 2A)	Thyroid MTC (100%)	MTC without other clinical manifestations of MEN 2A or MEN 2B
3. MEN 2B (also known as MEN3)	Thyroid MTC (~90%)	MTC: most common component, more aggressive and earlier onset than MEN 2A
	Adrenal medulla Pheochromocytoma (≥50%)	HTN, palpitations, headache, sweating
	Neurons Mucosal neuroma, intestinal ganglioneuromas (100%)	Chronic constipation; megacolon
	MSK Marfanoid	Marfanoid habitus (no aortic abnormalities)

Investigations

- MEN 1
  - laboratory
    - offer genetic testing to all patients with a clinical diagnosis of MEN1 and their first-degree relatives
    - gastrinoma: significantly elevated serum gastrin level with a low gastric pH; when gastrin is <10x ULN a secretin stimulation test may be required
    - insulinoma: hypoglycemia with insulin and C-peptide levels that are inappropriately high for the level of glucose
    - glucagonoma: elevated glucagon levels
    - pituitary tumours: assess GH, IGF-1, 24 h urine cortisol, and PRL levels (for over-production), TSH, free T4, 8 am cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)
    - hyperparathyroidism: serum Ca^{2+} and albumin, PTH levels; bone density scan (DEXA)
  - imaging
    - MRI for pituitary tumours, CT or MRI for gastrinoma, CT, MRI, or endoscopic ultrasound for insulinoma, parathyroid scan for parathyroid adenomas

- MEN 2
  - laboratory
    - genetic screening for RET mutations on chromosome 10 is the clinical standard of care in all individuals with a family history of MEN2 and has long-term benefits (early cure and prevention of MTC)
    - calcitonin levels (MTC); 24 h urine and serum metanephrines (pheochromocytoma); serum $Ca^{2+}$and PTH levels (hyperparathyroidism)
    - pentagastrin ± calcium stimulation test if calcitonin level is within reference range
    - FNA for thyroid nodules cytology
  - imaging
    - neck U/S or CT to identify thyroid nodules and lymphadenopathy
    - CT or MRI of adrenal glands to localize pheochromocytoma
    - metastatic disease generally picked up with cross-sectional imaging

Treatment

- MEN 1
  - medical
    - proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - cabergoline or other dopamine agonists to suppress PRL secretion and shrink prolactinomas
    - somatostatin analogue for control of symptoms of some of the GI neuroendocrine tumours such as glucagonoma
  - surgery for hyperparathyroidism when surgical indications met, functional pancreatic tumours (e.g. insulinoma, glucagonoma, gastrinoma), functioning pituitary tumours (except for prolactinomas where dopamine agonists are used), and nonfunctioning pituitary tumours if associated with mass effect
    - trans-sphenoidal approach is generally preferred for pituitary tumours, pituitary irradiation if surgery is not possible or has failed
- MEN 2
  - prophylactic thyroidectomy recommended in individuals with documented pathogenic RET mutation and an increased risk of aggressive MTC; if incident case, thyroidectomy after diagnosis of MTC
    - rule out presence of pheochromocytoma and hyperparathyroidism prior to thyroidectomy
    - thyroid hormone supplementation following total thyroidectomy
  - prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
  - pheochromocytoma managed with resection
    - α-blocker for at least 10-21 d for pheochromocytoma preoperatively
  - hyperparathyroidism managed with resection of parathyroid adenoma
    - hydration, IV bisphosphonates, or denosumab for severe hypercalcemia

Primary Hyperparathyroidism
Increased PTH secretion commonly due to parathyroid adenoma, lithium therapy; less often due to parathyroid carcinoma or parathyroid hyperplasia

Secondary Hyperparathyroidism
Elevated PTH in response to low calcium, often in patients with renal failure and osteomalacia (due to low or low-normal serum calcium levels)

Tertiary Hyperparathyroidism
Irreversible monoclonal outgrowth of parathyroid glands, usually in long-standing inadequately treated chronic renal failure on dialysis

PH is the most common cause of hypercalcemia in healthy outpatients. PH is most commonly related to a solitary adenoma or, less commonly, multiple gland hyperplasia. Surgical excision is the definitive treatment and is recommended for patients who have symptomatic hypercalcemia, loss in bone density, kidney stones, or renal failure. For asymptomatic disease, medical surveillance may be appropriate with annual serum calcium, creatinine, and bone mineral density (BMD)

For asymptomatic patients, surgery is recommended for those who meet ≥1 of the following criteria:

- Serum [Ca^{2+}] >0.25 mmol/L (1.0 mg/dL) above the upper limit of normal
- Skeletal involvement: 1) a fracture by Vertebral Fracture Assessment or vertebral x-ray, or 2) BMD T-score ≤−2.5 at any site
- Renal involvement: 1) eGFR or creatinine clearance <60 mL/min, or 2) nephrocalcinosis or nephrolithiasis by x-ray, ultrasound, or other imaging modality, or 3) hypercalciuria (>250 mg/day in women; >300 mg/day in men)
- Age <50 yr (no other indications are necessary; age <50 yr is a sufficient indication)

Calcium Homeostasis

- normal total serum Ca^{2+}: 2.2-2.6 mmol/L
- ionic/free Ca^{2+} levels: 1.15-1.31 mmol/L
- serum Ca^{2+} is 40% protein bound (mostly albumin), 45% ionized, and 15% complexed with PO_4^{3-} and citrate
- regulated mainly by: PTH and vitamin D, whose actions are on three main organs: GI tract, bone, and kidney

Table 27. Major Regulators in Calcium Homeostasis

Major Regulators	Source	Regulation	Net Effect
PTH	Parathyroid glands	Stimulated by low serum $Ca^{2+}$and high serum PO_4^{3-} Inhibited by high serum Ca^{2+}, high calcitriol, FGF23, and chronic low serum Mg^{2+}	↑ Ca^{2+} ↑ Calcitriol ↓ PO_4^{3-}
Calcitriol ($1,25\text{-}(OH)_2D_3$)	Dietary intake of cholecalciferol (D3) or ergocalciferol (D2) OR Synthesized from cholesterol: UV light on skin makes cholecalciferol (D3). Liver then converts it to calcidiol (25-(OH)D3) and kidneys convert it to calcitriol	Stimulated by: Low serum PO_4^{3-} High PTH Inhibited by: High serum PO_4^{3-} Low PTH Calcitriol (negative feedback) FGF23	↑ $Ca2+$ ↑ PO_4^{3-}
Calcitonin	Thyroid C cells	Stimulated by: Pentagastrin (GI hormone) and high serum $Ca2+$; inhibited by low serum Ca^{2+}	↓ Ca^{2+}(in pharmacologic doses) ↓ PO_4^{3-}
$MgCa^{2+}$	Major intracellular divalent cation	See Nephrology, NP16	Cofactor for PTH secretion
PO_4^{3-}	Intracellular anion found in all tissues	See Nephrology, NP15	↓ Ca^{2+}

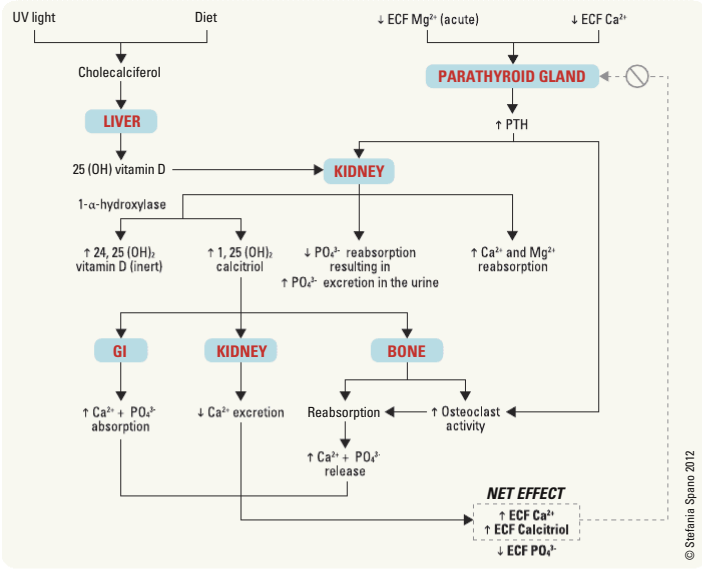


Figure 18. Parathyroid hormone (PTH) regulation

Total Ca^{2+} does not reflect ionized Ca^{2+} in the following circumstances:

- Abnormal albumin levels
- Critical illness
- Chronic hepatic failure/renal failure

When albumin is low, ionized calcium assessment should be performed

If ionized calcium is not available, total calcium can be corrected for albumin using this approximation:
Corrected Ca^{2+}(mmol/L) = measured Ca^{2+} + 0.02 (40 – albumin)

- for every decrease in albumin by 10, increase in $Ca^{2+}$by 0.2

Treatment of Hypercalcemia in Clinical Practice

In clinical practice, treatment is required if the patient has a) symptomatic hypercalcemia or b) extremely high levels of corrected Ca^{2+} . Laboratory cutoffs may not always be used

The symptoms and signs of hypercalcemia include: "Bones, stones, groans, and psychiatric overtones"

Hypercalcemia

Definition

- total corrected serum Ca^{2+} >2.6 mmol/L OR ionized Ca^{2+}>1.35 mmol/L

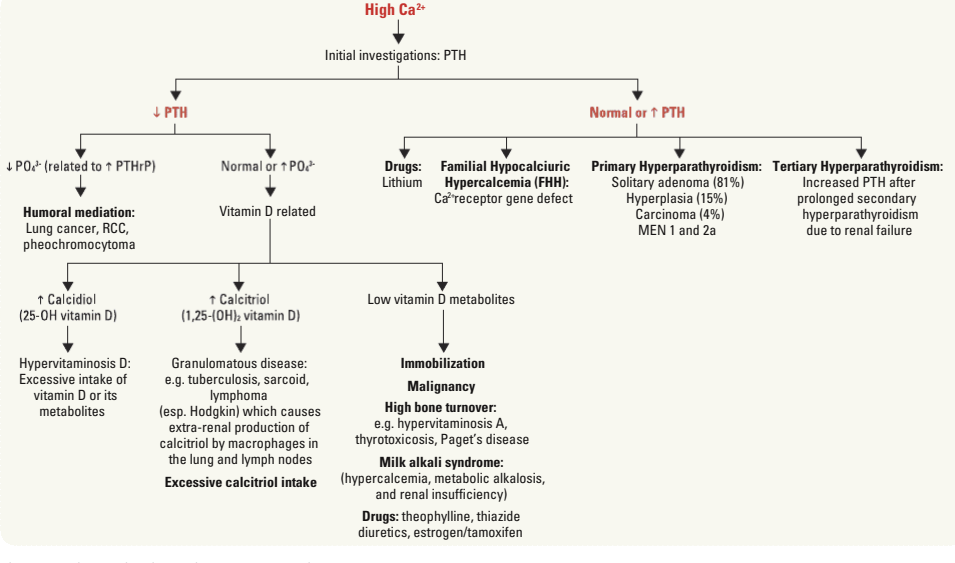

High Ca2+
Initial investigations: PTH
↓ PTH
Normal or ↑ PTH
↓ PO4 3- (related to ↑ PTHrP)
Normal or ↑ PO4 3-
Drugs: Lithium
Familial Hypocalciuric Hypercalcemia (FHH): Ca2+receptor gene defect
Primary Hyperparathyroidism: Solitary adenoma (81%) Hyperplasia (15%) Carcinoma (4%) MEN 1 and 2a
Tertiary Hyperparathyroidism: Increased PTH after prolonged secondary hyperparathyroidism due to renal failure
Humoral mediation: Lung cancer, RCC, pheochromocytoma
Vitamin D related
↑ Calcidiol (25-OH vitamin D)
↑ Calcitriol (1,25-(OH)2 vitamin D)
Low vitamin D metabolites
Hypervitaminosis D: Excessive intake of vitamin D or its metabolites
Granulomatous disease: e.g. tuberculosis, sarcoid, lymphoma (esp. Hodgkin) which causes extra-renal production of calcitriol by macrophages in the lung and lymph nodes
Excessive calcitriol intake
Immobilization
Malignancy
High bone turnover: e.g. hypervitaminosis A, thyrotoxicosis, Paget's disease
Milk alkali syndrome: (hypercalcemia, metabolic alkalosis, and renal insufficiency)
Drugs: theophylline, thiazide diuretics, estrogen/tamoxifen

Figure 19. Differential diagnosis of hypercalcemia

Approach to Hypercalcemia

1. is the patient hypercalcemic?
2. is the PTH high/normal or low?
3. if PTH is low, is phosphate high/normal or low?
4. if phosphate is high/normal, is the level of vitamin D metabolites high or low?

Clinical Features

- symptoms depend on the absolute Ca^{2+} value and the rate of its rise (may be asymptomatic)

Table 28. Symptoms of Hypercalcemia

Cardiovascular	GI	Renal	Rheumatological	MSK	Psychiatric	Neurologic
HTN Arrhythmia Short QT Deposition of Ca^{2+} on valves, coronary arteries, myocardial fibres	Constipation Anorexia Nausea Vomiting **(groans)** PUD Pancreatitis	Polyuria (Nephrogenic DI) Polydipsia **Nephrolithiasis (stones)** Renal failure (irreversible) Dehydration	Gout Pseudogout Chondrocalcinosis	Weakness Bone pain **(bones)**	>3 mmol/L (12 mg/dL) Increased alertness Anxiety Depression Cognitive dysfunction Organic brain syndromes >4 mmol/L (16 mg/dL) **Psychosis (moans)**	Hypotonia Hyporeflexia Myopathy Paresis

** **Hypercalcemic crisis (usually >4 mmol/L or 16 mg/dL):** primary symptoms include oliguria/anuria and mental status changes including somnolence and eventually coma → this is a medical emergency and should be treated immediately!

Treatment

- <3.0 mmol/L: mild, often asymptomatic and does not usually require urgent correction
- 3.0-3.5 mmol/L: may be well tolerated chronically and may not require immediate treatment but may be symptomatic and prompt treatment is usually indicated
- >3.5 mmol/L: severe hypercalcemia requiring urgent correction due to risk of dysrhythmia and coma
- aggressive treatment of acute symptomatic hypercalcemia
- next treat the underlying cause
- mild asymptomatic hypercalcemia: monitor and avoid thiazide, volume depletion, high Ca^{2+} diet, lithium, and bed rest

Table 29. Treatment of Acute Hypercalcemia/Hypercalcemic Crisis

Increase Urinary Ca^{2+} Excretion	FLUIDS, FLUIDS, FLUIDS! Isotonic saline (4-6 L) over 24 h ± loop diuretic (e.g. furosemide) but only if hypervolemic (urine output >200 mL/h) Calcitonin: 4 IU/kg IM/SC q12 h 8 IU/kg IM/SC q6 h Only works for 48 h, can develop tachyphylaxis Rapid onset within 4-6 h Before prescribing calcitonin, remember to ask about fish allergies
Diminish Bone Resorption	Bisphosphonates (treatment of choice) Suggest zoledronic acid 4 mg IV over 15 min or pamidronate 60-90 mg IV over 2 h Inhibits osteoclastic bone resorption, preventing calcium release from bone Effects on calcium levels are typically seen at 24-48 h after administration Calcitonin often given in conjunction with bisphosphonate, given rapid onset of effect Indicated in malignancy-related hypercalcemia (IV pamidronate or zoledronic acid used) If bisphosphonates are contraindicated (i.e. severe renal impairment), denosumab can be administered concurrently with calcitonin
Decrease GI Ca^{2+} Absorption	Corticosteroids can be used in hypercalcemia mediated by 1,25 vitamin D. Corticosteroids are potent inhibitors of 1a-hydroxylase and therefore, decrease calcitriol production by activated mononuclear cells (e.g. in lymphoma, granuloma) Effects will be seen in 2-5 d
Dialysis	Treatment of last resort Indication: severe malignancy-associated hypercalcemia and renal insufficiency or heart failure

The most common cause of hypercalcemia in hospital is malignancy-associated hypercalcemia

- Usually occurs in the later stages of disease
- Most commonly seen in lung, renal, breast, ovarian, and squamous tumours, as well as lymphoma and multiple myeloma

Mechanisms:

- Secretion of PTHrP which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption
- Cytokines in multiple myeloma
- Calcitriol production by lymphoma
- Osteolytic bone metastases direct effect
- Excess PTH in parathyroid cancer

Before prescribing calcitonin, remember to ask about fish allergies

Differential Diagnosis of Hypercalcemia

- Primary hyperparathyroidism
- Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2)
- Renal disease: tertiary hyperparathyroidism
- Drugs: calcium carbonate, milk alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication
- Familial hypocalciuric hypercalcemia
- Granulomatous disease: sarcoidosis, tuberculosis, Hodgkin's lymphoma
- Thyroid disease: thyrotoxicosis
- Adrenal disease: adrenal insufficiency, pheochromocytoma
- Immobilization

Acute Management of Hypercalcemia/ Hypercalcemic Crisis

- Volume expansion (e.g. NS IV 300-500 cc/h): initial therapy
- Calcitonin (SC): transient, partial response
- Bisphosphonate (IV): treatment of choice, adjust dose if CrCl <30 ml/min
- Corticosteroid: most useful in vitamin D toxicity, granulomatous disease, some malignancies
- Saline diuresis + loop diuretic (for volume overload): temporary measure

Hypocalcemia

Definition

- total corrected serum Ca^{2+} <2.2 mmol/L
- mild, asymptomatic: serum Ca^{2+} <1.9 mmol/L, ionized Ca^{2+} >0.8 mmol/L
- severe: serum Ca^{2+} <1.9 mmol/L and/or symptomatic

Table 30. Clinical Features of Hypocalcemia

Acute Hypocalcemia	Chronic Hypocalcemia
Paresthesia Laryngospasm (with stridor) Hyperreflexia Tetany Chvostek's sign (tap CN VII) Trousseau's sign (carpal spasm) ECG changes Delirium Psychiatric Sx: emotional instability, anxiety, and depression Seizure Note: tetany is a hallmark of hypocalcemia – can be mild or severe Mild: perioral numbness, paresthesia of hands and feet, muscle spasm Severe: carpopedal spasm, laryngospasm, focal/generalized seizures	CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson's, dystonia, hemiballismus, papilledema, pseudotumour cerebri CVS: prolonged QT interval ➔ Torsades de pointes (ventricular tachycardia) GI: steatorrhea ENDO: impaired insulin release SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition OCULAR: cataracts MSK: generalized muscle weakness and wasting

Approach to Hypocalcemia

1. is the patient hypocalcemic?
2. is the PTH high or low?
3. if PTH is high, is phosphate low or normal?
4. is the Mg^{2+} level low?

Approach to Treatment

1. rapidity of treatment depends on severity of symptoms and serum calcium level
   a) mild, asymptomatic
      - calcium supplementation (i.e. elemental calcium 1 g then 500 mg PO TID)

   b) severe and/or symptomatic
      - severe hypocalcemia is a medical emergency
      - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion
      - if positive Chvostek's and Trousseau or seizures, first give IV calcium bolus, i.e. 1 amp IV push, then run Ca^{2+} IV drip at 1-2 mg/kg/h
2. vitamin D replacement
   - needed for GI absorption of calcium; must use 1,25 vitamin D if PTH level low (hypoparathyroidism)
3. must treat concurrent hypomagnesemia or calcium will not normalize
4. if underlying cause is hypoparathyroidism, the goal is to raise Ca^{2+} to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH secretion

Signs and Symptoms of Acute Hypocalcemia
- Paresthesias: perioral, hands, and feet
- Chvostek's sign: percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles
- Trousseau's sign: inflation of a blood pressure cuff above systolic pressure for 3 min elicits carpal spasm and paresthesia

Hypomagnesemia can impair PTH secretion and action

Watch Out for:
- Volume depletion via diuresis
- Arrhythmias

Differential Diagnosis of Tetany
- Hypocalcemia
- Metabolic alkalosis (with hyperventilation)
- Hypokalemia
- Hypomagnesemia

Transient hypoparathyroidism (resulting in hypocalcemia) is common after total thyroidectomy (permanent in <3% of surgeries)

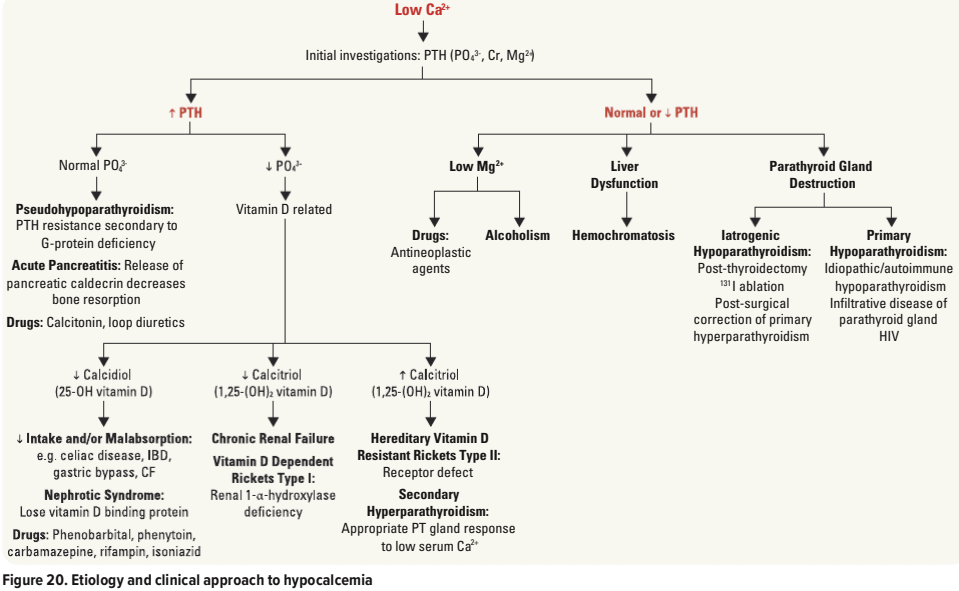

Low Ca^{2+}
Initial investigations: PTH (PO_4^{3-}, Cr, Mg^{2+})
↑ PTH
Normal or ↓ PTH
Normal PO_4^{3-}
↓ PO_4^{3-}
Low Mg^{2+}
Liver Dysfunction
Parathyroid Gland Destruction
Pseudohypoparathyroidism: PTH resistance secondary to G-protein deficiency
Acute Pancreatitis: Release of pancreatic caldecrin decreases bone resorption
Drugs: Calcitonin, loop diuretics
Vitamin D related
Drugs: Antineoplastic agents
Alcoholism
Hemochromatosis
Iatrogenic Hypoparathyroidism: Post-thyroidectomy ^{131}I ablation Post-surgical correction of primary hyperparathyroidism
Primary Hypoparathyroidism: Idiopathic/autoimmune hypoparathyroidism Infiltrative disease of parathyroid gland HIV
↓ Calcidiol (25-OH vitamin D)
↓ Calcitriol ($1,25-(OH)_2$ vitamin D)
↑ Calcitriol ($1,25-(OH)_2$ vitamin D)
↓ Intake and/or Malabsorption: e.g. celiac disease, IBD, gastric bypass, CF
Nephrotic Syndrome: Lose vitamin D binding protein
Drugs: Phenobarbital, phenytoin, carbamazepine, rifampin, isoniazid
Chronic Renal Failure
Vitamin D Dependent Rickets Type I: Renal 1-α-hydroxylase deficiency
Hereditary Vitamin D Resistant Rickets Type II: Receptor defect
Secondary Hyperparathyroidism: Appropriate PT gland response to low serum Ca^{2+}

Figure 20. Etiology and clinical approach to hypocalcemia

Metabolic Bone Disease

- see 2023 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis for details

Osteoporosis

Definition

- a condition characterized by decreased bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture
- BMD is measured at hip and lumbar spine, BMD T-score ≤-2.5 is diagnostic of osteoporosis
- osteopenia (low bone mass): BMD with T-score between –1.0 and –2.5

ETIOLOGY AND PATHOPHYSIOLOGY

Table 31. Secondary Osteoporosis

- Gastrointestinal diseases
  - Gastrectomy
  - Malabsorption (e.G. Celiac disease, IBD, bariatric surgery)
  - Chronic liver disease
  - Eating disorder
  - Poor nutrition
- Bone marrow disorders
  - Multiple myeloma
  - Lymphoma
  - Leukemia
- Endocrinopathies
  - Cushing's syndrome
  - Hyperparathyroidism
  - Hyperthyroidism
  - Premature menopause
  - Dm
  - Hypogonadism
- Malignancy
  - Secondary to chemotherapy
  - Myelomasevere: carpopedal spasm, laryngospasm, focal/ generalized seizures
- Rheumatologic disorders
  - Rheumatoid arthritis
  - SLE
  - Ankylosing spondylitis
- Drugs and chemotherapy
  - Corticosteroid therapy
  - Anti-epileptic drugs
  - Chronic heparin therapy
  - Androgen deprivation therapy
  - Aromatase inhibitors
- Renal disease
- Immobilization
- COPD (due to disease, tobacco, and glucocorticoid use)

Clinical Features

- always asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus, and wrist (see *Figure 21, E48*)
  - fragility fractures: fracture with fall from standing height or less (does not include fractures of hand, face, cervical spine, fingers, and toes)
  - Kyphosis: collapse fracture of vertebral bodies in thoracic region
  - x-ray: vertebral compression fractures (described as wedge fractures, require a minimum of 20% height loss), "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
  - pain, especially backache, associated with fractures

Approach to Osteoporosis

1. assess risk factors for osteoporosis on Hx and physical
2. decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women ≥65 yr (or younger if presence of risk factors, see *Table 33, E47*)
3. initial investigations
   - all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis if vertebral fractures, celiac workup, PTH, and 24 h urinary Ca^{2+}excretion to rule out additional secondary causes
   - 25-OH-vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture (or in individuals at moderate risk of fracture to help decide if they require medical therapy)
4. assess 10 yr fracture risk by combining BMD result and risk factors
   1) WHO Fracture Risk Assessment Tool (FRAX)
   2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
   - approach to management guided by 10 yr risk stratification into low, medium, and high-risk
5. for all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see *Table 34, E37*)

Corticosteroid Therapy is a Common Cause of Secondary Osteoporosis
Individuals receiving ≥7.5 mg of prednisone daily for over 3 mo should be assessed for bone-sparing therapy
Mechanism: increased resorption + decreased formation + increased urinary calcium loss + decreased intestinal calcium absorption + decreased sex steroid production

Calcium plus Vitamin D Supplementation and Risk of Fractures
Osteoporosis Int 2015;27:367-376
Purpose: To review trials of vitamin D and calcium therapy for reducing fracture risk in osteoporosis.
Study: Systematic review searching 2011-2015, inclusive, identified 8 RCTs totaling 30970 participants. RCTs reviewed included healthy adults and ambulatory older adults with medical conditions (excluding cancer). Vitamin D and calcium combination therapy was compared to placebo.
Results: Analysis of RCT data revealed that calcium plus vitamin D supplementation produced a statistically significant reduction in risk of total fractures (0.85; CI:0.73-0.98) and in hip fractures (0.70; CI:0.56-0.87). Subgroup analysis was significant for community dwelling or institutionalized patients.
Conclusions: Systematic analysis suggests that vitamin D and calcium therapy significantly decreases fracture risk. This study did not specifically look at individuals with osteoporosis. However, it still supports that vitamin D and calcium should continue to be used as preventive treatment for individuals at increased risk of fractures.

Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis
JAMA Netw Open 2019;2:e1917789
Purpose: To investigate if fracture risk is associated with supplementation with vitamin D alone or vitamin D in combination with calcium.
Study Selection: Observational studies with ≥200 fracture cases and RCTs with ≥500 participants that reported ≥10 incident fractures.
Results: Vitamin D supplementation alone was not associated with a reduced risk of any fracture or hip fracture (RR, 1.14; 95% CI, 0. 98-1.32). However, combined supplementation with vitamin D (400-800 IU daily) and calcium (1000-1200 mg daily) was associated with a 6% reduction in fracture risk (RR, 0.94; 95% CI, 0.89-0.99) and a 16% reduction of hip fracture risk (RR, 0.84; 95% CI, 0.72-0.97).
Conclusion: Vitamin D alone was not associated with reduced fracture risk but daily supplementation with a combination of vitamin D and calcium was.

Clinical Signs of Fractures or Osteoporosis
- Height loss >3 cm (Sn 92%)
- Weight <51 kg (Sp 97%)
- Kyphosis (Sp 92%)
- Tooth count <20 (Sp 92%)
- Grip strength
- Armspan-height difference >5 cm (Sp 76%)
- Wall-occiput distance >4 cm (Sp 92%)
- Rib-pelvis distance ≤2 finger breadth (Sn 88%)

Table 32. Indications for BMD Testing

Older Adults (age ≥50 yr)	Younger Adults (age <50 yr)
All women and men age ≥65 yr Menopausal women, and men 50-64 yr with clinical risk factors for fracture: Fragility fracture after age 40 Prolonged glucocorticoid use Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy) Parental hip fracture Vertebral fracture or osteopenia identified on x-ray Current smoking High alcohol intake Low body weight (<60 kg) or major weight loss (>10% of weight at age 25 yr) Rheumatoid arthritis Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, T1DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. inflammatory bowel disease)	Fragility fracture: Prolonged use of glucocorticoids Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy, anticonvulsants) Hypogonadism or premature menopause Malabsorption syndrome Primary hyperparathyroidism Other disorders strongly associated with rapid bone loss and/or fracture

Table 33. Osteoporosis Risk Stratification

Low-Risk 10 yr fracture risk <10%	Unlikely to benefit from pharmacotherapy; encourage lifestyle changes Reassess risk in 5 yr
Medium-Risk 10 yr fracture risk 10-20%	Discuss patient preference for management and consider additional risk factors Factors that warrant consideration for pharmacotherapy: Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray Previous wrist fracture in individuals ≥65 yr or with T-score ≤−2.5 Lumbar spine T-score much lower than femoral neck T-score Rapid bone loss Men receiving androgen-deprivation therapy for prostate cancer Women receiving aromatase-inhibitor therapy for breast cancer Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use Recurrent falls (defined as falling 2 or more times in the past 12 mo) Other disorders strongly associated with osteoporosis Repeat BMD and reassess risk every 1-3 yr initially
High-Risk 10 yr fracture risk >20%; OR Prior fragility fracture of hip or spine; OR More than one fragility fracture	Start pharmacotherapy (need to consider patient preference)

Treatment of Osteoporosis

Table 34. Treatment of Osteoporosis in Women and Men

Treatment for Both Men and Women	
Lifestyle	Diet: elemental calcium 1000-1200 mg/d; vitamin D 1000 IU/d Exercise: 3x30 min weight-bearing exercises, balance exercise, and aerobic exercise/wk Cessation of smoking, reduce caffeine intake Stop/avoid osteoporosis-inducing medications
Drug Therapy	
Bisphosphonate: inhibitors of osteoclasts	1st line in prevention of hip, nonvertebral, and vertebral fractures (Grade A): alendronate (PO), risedronate (PO), zoledronic acid (IV)
RANKL Inhibitors	Denosumab: 1st line in prevention of hip, nonvertebral, vertebral fractures (Grade A) *Denosumab should not be abruptly stopped/administration delayed. Increased risk of multiple vertebral fractures due to increased bone turnover on discontinuation. Used as an alternative initial treatment in postmenopausal women with osteoporosis who are at high risk for osteoporitic fractures.
Parathyroid Hormone Analogue	Teriparatide: 18-24 mo duration, followed by long-term anti-resorptive therapy with bisphosphonate or RANKL inhibitor
Sclerostin Inhibitors	Romosozumab: 12 mo duration
Treatment Specific to Post-Menopausal Women	
SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast	Raloxifene: evidence for prevention of vertebral fractures (Grade A) Advantages: prevents osteoporotic fractures (Grade A to B evidence), improves lipid profile, decreased breast cancer risk Disadvantages: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps
HRT: combined estrogen + progesterone (see Gynecology, GY36)	Indicated for vasomotor symptoms of menopause For most women, risks > benefits Combined estrogen/progestin prevents hip, vertebral, total fractures Increased risks of breast cancer, cardiovascular events, and DVT/PE

Online Clinical Tools
FRAX
www.shef.ac.uk/FRAX/tool.aspx
CAROC
www.osteoporosis.ca/multimedia/pdf/CAROC.pdf

Prevention - Hip

Alendronate	0.61 RR (0.42-0.90)
Risedronate	0.73 RR (0.58-0.92)
Denosumab	0.56 RR (0.35-0.90)
Teriparatide	0.64 RR (0.25-1.68)
Romosozumab	0.44 RR (0.24-0.79)

Prevention - Nonvertebral

Alendronate	0.84 RR (0.74-0.94)
Risedronate	0.78 RR (0.68-0.89)
Denosumab	0.80 RR (0.67-0.96)
Teriparatide	0.62 RR (0.47-0.80)
Romosozumab	0.67 RR (0.53-0.86)

Prevention - Vertebral

Alendronate	0.57 RR (0.45-0.71)
Risedronate	0.61 RR (0.48-0.78)
Denosumab	0.32 RR (0.22-0.45)
Teriparatide	0.27 RR (0.19-0.38)
Romosozumab	0.33 RR (0.22-0.49)

Factors Necessary for Mineralization
- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial
JAMA 2019;322:736-45
Purpose: To investigate the effects of vitamin D supplementation on volumetric BMD and strength.
Methods: 311 healthy adults (ages 55-70) without osteoporosis, with baseline concentrations of 25-hydroxyvitamin D of 30-125 nmol/L, were randomized to receive daily doses of 400 IU, 4000 IU, or 10000 IU vitamin D3 for 3 years. For participants with calcium dietary intake <1200 mg/d, supplementation was provided. Primary Outcome: Total volumetric BMD at radius and tibia.
Results: Compared with the 400 IU group, radial volumetric BMD was significantly lower for the 4000 IU group (-3.9 mg HA/cm3; 95% confidence interval (CI), -6.5 to -1.3) and 10000 IU group (-7.5 mg HA/cm3; 95% CI, -10.1 to -5.0) with mean % change of -1.2% (400 IU), -2.4% (4000 IU), and -3.5% (10000 IU). Compared with the 400 IU group, tibial volumetric BMD differences were -1.8 mg HA/cm3 (95% CI, -3.7 to 0.1) (4000 IU) and -4.1 mg HA/cm3 (95% CI, -6.0 to -2.2) (10000 IU), with mean % change values of -0.4% (400 IU), -1.0% (4000 IU), and -1.7% (10000 IU).
Conclusion: In healthy adults, supplementation with daily 4000 IU or 10000 IU vitamin D for 3 years was associated with lower radial BMD compared with 400 IU. 10000 IU was associated with lower tibial BMD. There were no apparent benefits of high-dose vitamin D supplementation for bone health.

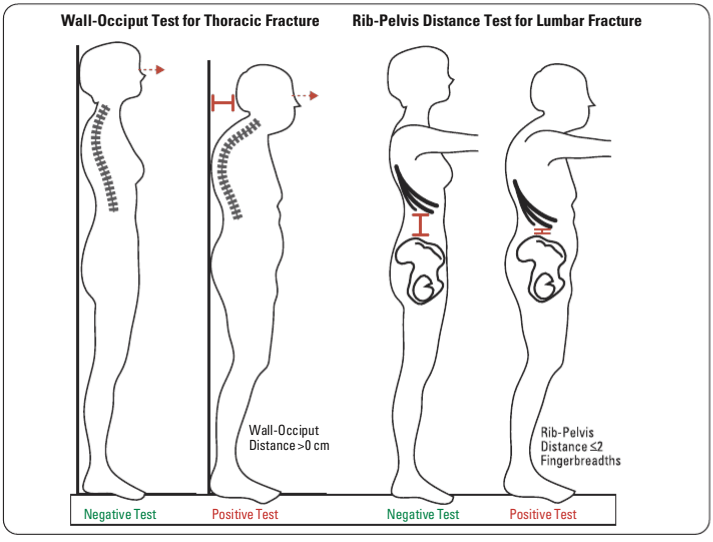


Figure 21. Physical examination test for vertebral fractures

Osteomalacia and Rickets

Definition

- osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue prior to epiphyseal closure: rickets (in childhood), osteomalacia (in adulthood)

Etiology and Pathophysiology

Vitamin D Deficiency

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)
- loss of vitamin D binding protein
  - nephrotic syndrome
- decreased 1-α-25 hydroxylation
  - hypoparathyroidism
- renal failure

Mineralization Defect

- abnormal matrix
  - osteogenesis imperfecta
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - aluminum, high dose fluoride, anticonvulsants

Calcium Deficiency

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption
- hypercalciuria (in combination with renal phosphate wasting)

Hypophosphatemia

- gastrointestinal: poor nutritional intake, chronic diarrhea, excessive phosphate binders
- renal phosphate wasting
  - tumour-induced osteomalacia
  - Fanconi syndrome
  - X-linked/autosomal dominant/recessive hypophosphatemic rickets

Matrix Abnormalities
- type IV osteogenesis imperfecta
- fibrogenesis imperfecta ossium
- axial osteomalacia

Table 35. Clinical Features of Rickets and Osteomalacia

Rickets	Osteomalacia
Skeletal pain and deformities, bow-legged	Not as severe
Fracture susceptibility	Diffuse skeletal pain
Weakness and hypotonia	Bone tenderness
Disturbed growth	Fractures
Rachitic rosary (prominent costochondral junctions)	Gait disturbances (waddling)
Harrison's groove (indentation of lower ribs)	Proximal muscle weakness
Hypocalcemia	Hypotonia

Investigations

Table 36. Laboratory Findings in Osteomalacia and Rickets

Disorder	Serum Phosphate	Serum Calcium	Serum ALP	Other Features
Vitamin D Deficiency	Decreased	Decreased to normal	Increased	May have decreased calcitriol
Hypophosphatemia	Decreased	Normal	Increased	
Proximal Renal Tubular Acidosis	Decreased	Normal	Normal	Associated with hyperchloremic metabolic acidosis
Conditions Associated with Abnormal Matrix Formation	Normal	Normal	Normal	

- radiologic findings
  - pseudofractures (i.e. Looser zones), fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profundus hip deformity
- bone biopsy: usually not necessary but considered the gold standard for diagnosis

Treatment
- definitive treatment depends on the underlying cause
- vitamin D supplementation
- PO_4^{3-} supplements if low serum PO_4^{3-}, Ca^{2+} supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis

KDIGO 2017 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease
- Kidney Inter Suppl 2017;7(1):1-60
- Recommendations for Metabolic Bone Disease (MBD) in Chronic Kidney Disease (CKD)

Screening
- In CKD patients with evidence of CKD-MBD and/or risk factors for osteoporosis, perform BMD testing to assess fracture risk if results will impact treatment decisions
- In patients with CKD-BMD, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions

Management
- Treatment of CKD-MBD should be based on serial assessments of PO_4^{3-}, Ca^{2+}, and PTH levels, considered together
- Suggest lowering elevated P043- levels towards the normal range
- Avoid hyperglycemia in adult patients and maintain serum Ca^{2+} in age-appropriate normal range in children

Renal Osteodystrophy

Definition
- changes to mineral metabolism and bone structure secondary to CKD
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoids
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology
- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)2 vitamin D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Clinical Features
- soft tissue calcifications, necrotic skin lesions if vessels involved
- osteodystrophy, generalized bone pain, and fractures
- pruritus
- neuromuscular irritability and tetany may occur (with low serum calcium)
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations
- serum Ca^{2+} corrected for albumin, PO_4^{3-}, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy (gold standard; only done if results inform treatment)

Treatment
- prevention
- maintenance of normal serum Ca^{2+} and PO_4^{3-} by restricting PO_4^{3-} intake to 1 g once daily
- Ca^{2+} supplements; PO_4^{3-} binding agents (calcium carbonate, aluminum hydroxide)
- activated vitamin D (calcitriol) with close monitoring to avoid hypercalcemia and metastatic calcification
- bisphosphonates and denosumab are not often used for treatment (can worsen the adynamic components of renal osteodystrophy) as they are contraindicated at low eGFRs; bone biopsy may indicate if there are signs of increased bone turnover amenable to bisphosphonates

Paget's Disease of Bone

Definition
- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology
- 3% of the population, 10% of population >80 y/o
- consider Paget's disease of bone in older adults with elevated ALP but normal GGT

Etiology and Pathophysiology
- postulated to be related to a slowly progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis
- osteogenic sarcoma
- multiple myeloma
- fibrous dysplasia
- osteitis fibrosa cystica
- metastases

Clinical Features
- usually asymptomatic (routine x-ray finding or elevated serum ALP with normal LFTs)
- 3 characteristic findings: osteolytic lesions, cortical thickening, pseudofractures (small fissures which develop in the convex surface of long bone)
- most commonly affects: skull, thoracolumbar spine, pelvis, and long bones of lower extremities
- severe bone pain (e.g. pelvis, femur, tibia)
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- increased risk of osteosarcoma and giant cell tumours

Investigations
- laboratory
  - high serum ALP, normal or high Ca^{2+}, normal PO_4^{3-}
  - normal tests LFTs (prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), albumin, bilirubin)
  - elevated procollagen type I N-terminal propeptide (PINP) (bone formation marker)
- imaging
  - plain x-ray of skull and facial bones, abdomen, and tibiae are recommended as initial screening in patients suspected to have Paget's
  - confirmation on x-ray required for diagnosis
    - denser bone with cortical thickening
    - characteristic findings: osteolytic lesions, cortical thickening, and pseudofractures
    - burned-out Paget's disease: when the disease has been present for a long time
  - bone scan, to evaluate the extent of disease and identify asymptomatic sites, in addition to targeted x-ray are recommend to fully and accurately define the extent of metabolically active Paget's disease
  - MRI or CT are not recommended for diagnosis, but can be used to assess disease complications, particularly if malignancy is suspected

Table 37. Paget's Disease-Related Signs

Signs	Descriptions
Tam o'Shanter	Appearance of advanced Paget's disease of the skull – overall enlargement of cranium, skull falling over the facial bones
Blade of grass	Lucent leading edge in a long bone seen in lytic phase of Paget's
Osteoporosis circumscripta	Radiolucent regions of the skull
Jigsaw pattern bone or mosaic pattern bone	Thickened, disorganized trabeculae lead to areas of sclerosis
Picture frame vertebra	Cortex of vertebral body is thickened
Cotton wool appearance of bone	Results from thickened, disorganized trabeculae that lead to areas of sclerosis
Banana fracture	Horizontal pathological fracture seen in bones deformed by Paget's
Looser zones	Wide, transverse lucencies traversing through a bone
Ivory vertebra	Diffuse and homogenous increase in opacity of a vertebral body

Complications

- local
  - fractures; osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
    - indicated by marked bone pain, new lytic lesions, and suddenly increased ALP
- systemic
  - hypercalcemia and nephrolithiasis
  - high output CHF due to increased vascularity

Treatment

- goals: decrease pain, decrease rate of remodelling
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
- treat medically if symptomatic or asymptomatic with ALP >3x normal or planned surgery
  - bisphosphonates, e.g. zoledronic acid 5 mg IV per yr (preferred) OR alendronate 40 mg PO once daily x 6 mo OR risedronate 30 mg PO once daily x 3 mo
  - calcitonin 50-100 U/d SC if unable to tolerate bisphosphonates
- surgery for fractures, deformity, degenerative changes
- joint replacement surgery and osteotomy are recommended for the treatment of osteoarthritis resistant to medical therapy in patients with Paget's

Male Reproductive Endocrinology

Androgen Regulation

- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

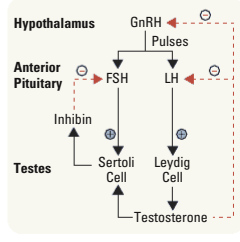


Figure 22. Hypothalamo-pituitary-gonadal axis

Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm in adult)
  - can use orchidometer to measure testicular volume (12-25 mL = adult size)
- LH, FSH, total, bioavailable, and/or free testosterone
- semen analysis
  - semen volume, sperm concentration, morphology, and motility are the most commonly used parameters
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility

• see Urology, U37
- deficiency in gametogenesis or testosterone production

Etiology

- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure), and idiopathic

Diagnosis of Testosterone Deficiency Syndrome (i.e. adult onset primary hypogonadism)

- requires clinical manifestations of testosterone deficiency (see sidebar) AND documented testosterone levels below the laboratory reference range (confirmed on 2 separate analyses, test needs to be done at 8-9 am when testosterone is usually at its peak)
- rule out secondary causes

Two Distinct Features of Primary Hypogonadism

The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level

Likely to be associated with gynecomastia

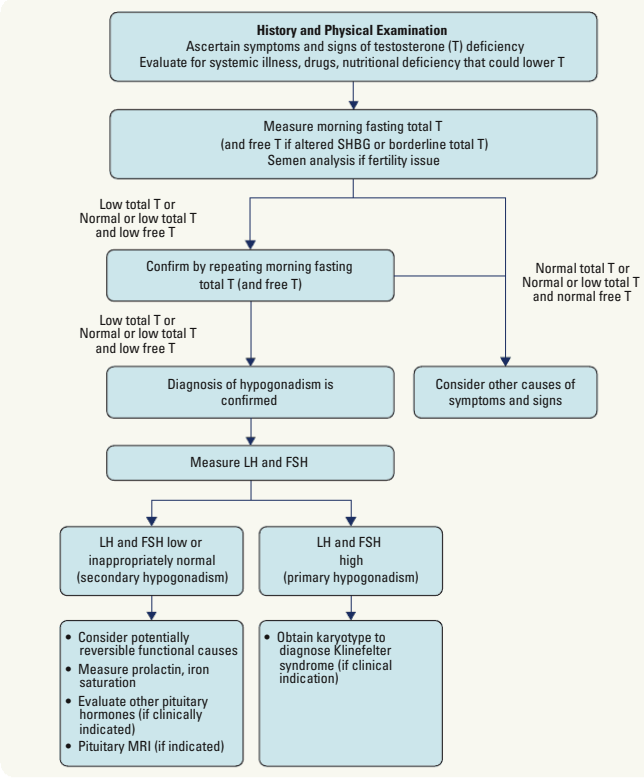

History and Physical Examination
Ascertain symptoms and signs of testosterone (T) deficiency
Evaluate for systemic illness, drugs, nutritional deficiency that could lower T
Measure morning fasting total T
(and free T if altered SHBG or borderline total T)
Semen analysis if fertility issue
Low total T or
Normal or low total T
and low free T
Confirm by repeating morning fasting
total T (and free T)
Normal total T or
Normal or low total T
and normal free T
Low total T or
Normal or low total T
and low free T
Diagnosis of hypogonadism is
confirmed
Consider other causes of
symptoms and signs
Measure LH and FSH
LH and FSH low or
inappropriately normal
(secondary hypogonadism)
LH and FSH
high
(primary hypogonadism)
• Consider potentially reversible functional causes
• Measure prolactin, iron saturation
• Evaluate other pituitary hormones (if clinically indicated)
• Pituitary MRI (if indicated)
• Obtain karyotype to diagnose Klinefelter syndrome (if clinical indication)

Figure 23. Diagnostic approach to testosterone deficiency

Approach to Male Infertility

Infertility: failure of a couple to conceive after 12 mo of regular intercourse without use of contraception in women <35 yr of age; after 6 mo of regular intercourse without use of contraception in women ≥35 yr

History

- Partner status regarding infertility
- Length of time for attempt to conceive
- Prior successes with other partners
- Ejaculation problems
- Frequency of intercourse
- Previous Surg, Med Hx, STI Hx
- Hx orchitis? Cryptorchidism?
- Hx toxic exposure?
- Medications
- Alcohol and illicit drug use
- Heat exposure: bath, sauna, whirlpool
- Smoking
- Other: validated questionnaires (e.g. ADAM questionnaire)

Physical Examination

- General (height, weight, gynecomastia, masculine)
- Testicular size and consistency
- Varicocele?
- Pituitary disease?
- Thyroid disease?

Investigations

- Semen analysis x 2 (sperm count, morphology, motility)
- Scrotal/testicular U/S (look for varicocele)
- Blood work: LH, FSH, testosterone, PRL, thyroid function tests, DNA fragmentation of sperm, karyotype, Y chromosome deletion
- Test female partner (see Gynecology, GY24)

Treatment

- No specific therapy for majority of cases
- Treat specific causes
- Consider: intrauterine insemination, in vitro fertilization (IVF), therapeutic donor insemination, testicular aspiration of sperm, adoption

Table 38. Classification and Features of Hypogonadism

	Hypergonadotropic Hypogonadism (Primary Hypogonadism)	Hypogonadotropic Hypogonadism (Secondary Hypogonadism)
Definition	Primary testicular failure ↑ LH and FSH ↓ testosterone and sperm count	Hypothalamic-pituitary axis failure ↓ LH and FSH (LH sometimes inappropriately normal) ↓ testosterone and sperm count
Etiology	Congenital Chromosomal defects (Klinefelter, Noonan) Cryptorchidism Disorders of sexual development (DSD) Bilateral anorchia (vanishing testicle syndrome) Myotonic dystrophy Mutation of FSH or LH receptor gene Disorders of androgen synthesis Germ cell defects Sertoli cell only syndrome Leydig cell aplasia/failure Infection/Inflammation Orchitis – tuberculosis, lymphoma, mumps, leprosy Genital tract infection Physical factors Trauma, heat, irradiation, testicular torsion, varicocele Drugs Cannabis, alcohol, chemotherapy, ketoconazole, glucocorticoid, spironolactone	Congenital Kallman's syndrome Prader-Willi syndrome Abnormal subunit of LH or FSH Infection Tuberculosis, meningitis Endocrine Adrenal androgen excess Cushing's syndrome Hypo or hyperthyroidism Hypothalamic-pituitary disease (tumour, hyperprolactinemia, hypopituitarism) Drugs Alcohol, cannabis, spironolactone, ketoconazole, GnRH agonists, androgen/estrogen/progestin use, chronic narcotic use Chronic illness Cirrhosis, chronic renal failure, AIDS Sarcoidosis, Langerhan's cell histiocytosis, hemochromatosis Critical illness Surgery, MI, head trauma Obesity Idiopathic
Diagnosis	**Testicular size and consistency (soft/firm)** Sperm count LH, FSH, total, and/or bioavailable testosterone hCG stimulation (mainly used in pediatrics) Karyotype	**Testicular size and consistency (soft/firm)** Sperm count LH, FSH, total, and/or bioavailable testosterone Prolactin levels (and pituitary panel - T4/8 AM cortisol) Fe, transferrin MRI of hypothalamic-pituitary region

Treatment
- goal: testosterone replacement (improve libido, muscle mass, strength, body hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
  - side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy, uncertain effects on cardiac events/mortality in older men
  - contraindicated in men with prostate or breast cancer, a palpable prostate nodule, prostate-specific antigen (PSA) >4 ng/mL, elevated hematocrit, untreated severe obstructive sleep apnea (OSA), severe lower urinary tract symptoms (LUTS), uncontrolled CHF, MI, or stroke in last 6 mo, or thrombophilia
  - not suggested in men >65 yr, in men with T2DM with low testosterone concentrations, or in men planning fertility in the near term
  - testosterone therapy only to treat symptoms of hypogonadism, often results in decreased spermatogenesis (and reduced sperm counts) by further suppression of hypothalamic-pituitary-gonadal axis and suppression of endogenous testosterone production
- goal: fertility
  - treat underlying cause
  - GnRH agonist if hypothalamic dysfunction with intact pituitary, administered SC in pulsatile fashion using an external pump
  - hCG ± recombinant follicle stimulating hormone (rFSH) in cases of either hypothalamic or pituitary lesions
  - dopamine agonist (e.g. bromocriptine, cabergoline) if prolactinoma
  - testicular sperm extraction (TESE) or microscopic sperm extraction (MICROTESE) – only if testicular tissues are not functioning

Other Causes of Male Infertility
- hereditary disorders: Kartagener syndrome (primary ciliary dyskinesia), cystic fibrosis (absence of the vas deferens)
- anatomy: hypospadias, retrograde ejaculation
- obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- surgery: transurethral resection of the prostate (TURP), radical prostatectomy, orchiectomy

DEFECTS IN ANDROGEN ACTION

Etiology
- complete androgen insensitivity (CAIS)
- partial androgen insensitivity (PAIS)
- 5-α-reductase deficiency
- mixed gonadal dysgenesis
- defects in testosterone synthesis
- infertile male syndrome
- undervirilized fertile male syndrome

Clinical Features
- depends on age of onset

Table 39. Effects of Testosterone Deficiency

First Trimester *in utero*	Incomplete virilization of external genitalia (ambiguous genitalia) Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphrodism)
Third Trimester *in utero*	Micropenis Cryptorchidism (failure of normal testicular descent)
Prepuberty	Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair) Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones) Poor muscle development, reduced peak bone mass
Postpuberty	Decrease in energy, mood, and libido Fine wrinkles in corners of mouth and eyes Decrease in pubic/axillary hair, hematocrit, muscle mass, strength, and BMD

Adapted from: UpToDate, 2010; Cecil's Essentials of Medicine

Treatment
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)

Erectile Dysfunction

- see Urology, U33

Gynecomastia

Definition

- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- physiologic gynecomastia – trimodal distribution in neonatal, pubertal, and older males
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals

Pubertal Gynecomastia

- This benign condition peaks between ages 13-14 and spontaneously regresses in 90% of cases within 2 yr
- Waiting is often the best approach

Etiology

- physiologic gynecomastia – trimodal distribution in neonatal, pubertal, and older males
- drugs spironolactone, cimetidine, ketoconazole, recombinant human GH, hCG, estrogens, antiandrogens, GnRH agonists, 5-α-reductase inhibitors, androgen deprivation therapy (ADT)
- surgical ADT (orchiectomy) for prostate cancer
- starvation and refeeding
- male hypogonadism
- cirrhosis – due to reduced ability of liver to metabolize and inactivate estrogens
- treatment of HIV infection – due to fat tissue as part of lipodystrophy
- herbal products – plant-derived oils such as lavender and tea tree oil
- idiopathic
- testicular neoplasms
- CKD
- other rare causes: feminizing adrenal tumours, disorders of sex development, ectopic hCG, familial prepubertal gynecomastia
- hyperthyroidism

Causes of Gynecomastia

DOC TECH
Drugs (especially antiandrogens, i.e. spironolactone)
Other
Congenital (Klinefelter syndrome)
Tumour (especially germ cell tumours)
Endocrine (hyperthyroidism)
CHronic disease (cirrhosis, CKD)

Pathophysiology

- hormonal imbalance due to:
  - increased estrogen activity
    - increased production, or increased availability of estrogen precursors for peripheral conversion to estrogen, or decreased metabolism/inactivation
  - decreased androgen activity
    - decreased androgen production, binding of androgen to sex hormone binding globulin (SHBG), or androgen receptor blockage

Drugs Causing Gynecomastia

DISCKO
Digoxin
Isoniazid
Spironolactone
Cimetidine
Ketoconazole
Oestrogen/anti-testosterone

History

- recent change in breast characteristics
- pain
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction

Occurrence of Gynecomastia

3 Peaks	% Affected
Infancy	60-90
Puberty	4-69
Ages 50-80	24-65

Physical Exam

- signs of feminization
- breast
  - rule out red flags suggesting breast cancer: unilateral, eccentric, hard or fixed mass, skin dimpling or retraction, and nipple discharge (especially bloody) or crusting
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue
- genito-urinary exam
- stigmata of liver or thyroid disease

Investigations

- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated, need to locate the primary tumour); however not all investigations are required for every case of gynecomastia
- if the differentiation between gynecomastia and breast carcinoma cannot be made on the basis of clinical findings alone, the patient should undergo diagnostic mammography, which has 90% sensitivity and specificity for distinguishing malignant from benign breast diseases
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)

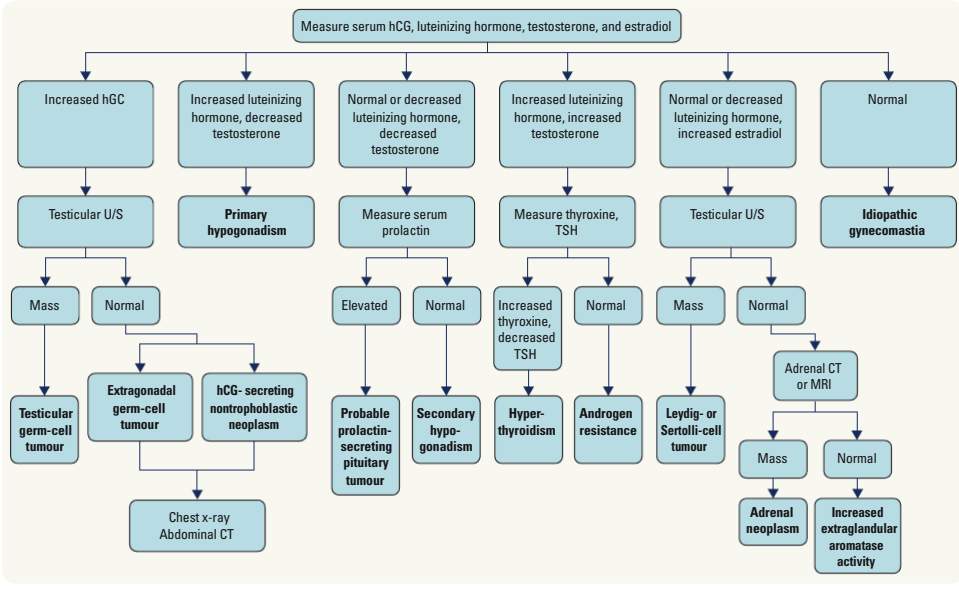


Figure 24. Approach to investigating gynecomastia

Treatment

- initial observation for most men with gynecomastia (after stopping offending medications and treating underlying cause)
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen has most evidence for benefit
- surgical
  - longstanding (>12 mo, fibrotic), discomfort, or causing psychological distress

Female Reproductive Endocrinology

- see Gynecology, GY23

Paraneoplastic Syndrome

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

Table 40. Clinical Features

Syndrome Class	Symptoms/Syndrome	Associated Malignancies	Mechanism
Endocrine	Cushing's syndrome Weight gain in trunk/face/between shoulders, stretch marks, easy bruising, slow wound healing, acne, hirsutism, irregular menses, decreased libido	Small-cell lung cancer Pancreatic carcinoma Neural tumours Thymoma	Ectopic ACTH and ACTH-mimicking substance secretion
	Syndrome of inappropriate ADH secretion (SIADH) Oliguria, hyponatremia, nausea/vomiting, headaches, confusion, fatigue, irritability, muscle weakness/cramps, seizures	Small-cell lung cancer CNS malignancies	Antidiuretic hormone secretion
	Hypercalcemia "Stones, bones, abdominal moans, psychic overtones"	Lung cancer Breast carcinoma Renal cell carcinoma Multiple myeloma Ovarian carcinoma	PTH-related protein, transforming growth factor alpha (TGF-α), tumour necrosis factor (TNF) secretion
	Hypoglycemia Tachycardia, headache, tremor, diaphoresis, fatigue, dizziness	Hepatocellular carcinoma Fibrosarcoma insulinoma	Insulin or insulin-like substance secretion
	Carcinoid Flushing, diarrhea, shortness of breath, tachycardia	Gastrointestinal neuroendocrine tumours	Serotonin, bradykinin secretion
Neurologic	Lambert-Eaton myasthenic syndrome (LEMS) Muscle weakness in limbs	Small-cell lung cancer	Ab interferes with acetylcholine (ACh) release
	Myasthenia gravis Fluctuating muscle weakness and fatigability	Thymoma	Ab interferes with ACh release
	Paraneoplastic limbic encephalitis Depression, seizures, short-term memory loss	Small-cell lung cancer	Unknown
Renal	Hypokalemic nephropathy Polyuria, polydipsia, anorexia, nausea/vomiting	Small-cell lung cancer	Ectopic ACTH and ACTH-like substance secretion
	Nephrotic syndrome Edema, hypertension, hematuria, immune impairment, hypercoagulability	Lymphoma Melanomas	Immunocomplex sedimentation in nephrons
GI	Watery diarrhea	MTC VIPoma	Calcitonin, prostaglandin secretion VIP secretion
Hematologic	Erythrocytosis	Renal cell carcinoma Hepatocellular carcinoma	Erythropoietin (EPO) production
Rheumatologic	SLE "SOAP BRAIN MD": serositis (pleuritis, pericarditis), oral ulcers, arthritis, photosensitivity, blood (low counts), renal (protein), ANA+, immunologic (DS DNA, etc.), neurologic (psych, seizures), malar rash, discoid rash	Lymphomas Lung cancer Breast carcinoma Gonadal carcinoma	Anti-nuclear Ab production
	Scleroderma Diffuse thickening of the skin, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia)	Breast carcinoma Lung cancer Uterine cancer	Anti-nuclear Ab production

Investigations

- CBC, electrolytes, creatinine, LFTs, ALP, erythrocyte sedimentation rate (ESR), CRP, serum/urine electrophoresis
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, positron emission tomography (PET) scan
- ± endoscopy

Treatment

- treat underlying tumour: surgery, radiation, chemotherapy
- treat immune-mediated disorder: intravenous immunoglobulin (IVIG), steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)

Common Medications

Diabetes Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects	Comments
Biguanide	Sensitizes peripheral tissues to insulin → increases glucose uptake Decreases hepatic glucose production by simulation of hepatic AMP-activated protein kinase (AMPK)	metformin	Glucophage® Glumetza®		500 mg once daily titrated to 2000 mg/d maximum (split BID unless extended release)	T2DM Improves both fasting and postprandial hyperglycemia Also ↓ TG	ABSOLUTE: Moderate to severe liver dysfunction Moderate renal dysfunction GFR <30 mL/min Cardiac dysfunction	GI upset (abdominal discomfort, bloating, diarrhea) Vitamin B_{12} deficiency	↓ A1c 1.0-1.5% Weight neutral Negligible risk of hypoglycemia as monotherapy
Insulin Secretagogue	Stimulates insulin release from β cells by causing K^+ channel closure → depolarization → Ca^{2+}-mediated insulin release Use in nonobese T2DM	sulfonylureas: glyburide gliclazide glimepiride	 Diabeta® Euglucon® Diamicron® Diamicron® MR Amaryl®	 Micronase® Glynase PreTab®	 2.5-5.0 mg/d titrated to >5 mg BID Max: 20 mg/d 40-160 mg BID 30-120 mg once daily 1-8 mg once daily	T2DM, taken with meals	ABSOLUTE: Moderate to severe liver dysfunction RELATIVE (glyburide and glimepiride): Adjust dose in mild to moderate kidney dysfunction and avoid in severe kidney dysfunction Avoid glyburide in the elderly INTERACTIONS: Do not combine with a non-sulfonylurea insulin secretagogue or preprandial insulin	Hypoglycemia Weight gain	↓ A1c 0.8% Gliclazide lowest incidence of hypoglycemia
Meglitinides	Stimulates insulin release from β cells by causing K^+ channel closure → depolarization → Ca^{2+}-mediated insulin release	non-sulfonylureas: repaglinide nateglinide	 GlucoNorm® Starlix®	 Prandin®	 0.5-4 mg TID 60-120 mg TID	Short t1/2 of 1 h causes brief but rapid ↑ in insulin, therefore effective for postprandial control	ABSOLUTE: Severe liver dysfunction INTERACTIONS: Do not combine with a sulfonylurea or preprandial insulin	Hypoglycemia (less than sulfonylurea) Weight gain	↓ A1c 0.7% for repaglinide and 0.5-1.0% for nateglinide Costly Must be dosed with meals
Insulin Sensitizers (thiazolidinedione)	Sensitizes peripheral tissues to insulin → increases glucose uptake Decreases FFA release from adipose Binds to nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ)	rosiglitazone pioglitazone	Avandia® Actos®		2-8 mg once daily 15-45 mg once daily	T2DM – not as initial therapy	ABSOLUTE: New York Heart Association (NYHA) > class II CHF, bladder cancer INTERACTIONS: Do not combine with insulin	Peripheral edema CHF Anemia Fluid retention and CHF Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing) Increased risk of bladder cancer with pioglitazone Fractures Mild increase in LDL	↓ A1c 0.8% Delayed maximum efficacy (6-12 wk) NOTE: This class of medication is rarely used anymore due to side effects and concerns about potential increased cardiovascular (CV) mortality
α-Glucosidase Inhibitor	↓ carbohydrate GI absorption by inhibiting brush border α-glucosidase	acarbose	Glucobay®	Precose®	25 mg once daily titrated to 100 mg TID	↓ postprandial hyperglycemia	ABSOLUTE: Inflammatory bowel disease Severe liver dysfunction	Flatulence Abdominal cramps Diarrhea	↓ A1c 0.6% Not recommended as initial therapy in patients with HbA1c >8.5%
Dipeptidyl Peptidase-IV (DPP-IV) Inhibitor	Inhibits degradation of endogenous antihyperglycemic incretin hormones Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emptying	sitagliptin saxagliptin linagliptin	Januvia® Onglyza™ Trajenta®		100 mg once daily 2.5-5 mg once daily 5 mg once daily		ABSOLUTE (sitagliptin): T1DM DKA RELATIVE (sitagliptin and saxagliptin): Use with dose reduction in kidney dysfunction	Nasopharyngitis Upper respiratory tract infection (URTI) Headache Pancreatitis Stevens Johnson syndrome Bullous pemphigoid	↓ A1c 0.7% Weight neutral Expensive Negligible risk of hypoglycemia as monotherapy

Diabetes Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects	Comments
Glucagon-Like Peptide (GLP)-1 Analogue	Binds to GLP-1 receptor to promote insulin release Insulinotropic effect suppressed as plasma glucose <4 mmol/L Slows gastric emptying, suppresses inappropriately elevated glucagon levels Causes β-cell regeneration and differentiation *in vitro*	exenatide liraglutide semaglutide dulaglutide	Byetta® Victoza® Rybelsus PO/ Ozempic SC® Trulicity®		5-10 µg SC BID 1 h before meals 0.6-1.8 mg once daily SC 3-14 mg once daily PO, 0.25-1 mg once weekly SC 0.75-1.5 mg/ wk SC		ABSOLUTE: T1DM DKA Acute pancreatitis Hx Multiple endocrine neoplasia syndrome type 2 MTC RELATIVE: Gastroparesis End stage renal disease (ESRD) Personal or family history of MTC	N/V, diarrhea Dizziness, headache Muscle weakness Anti-exenatide antibodies Pancreatitis	↓ A1c 1.0% Weight loss Negligible risk of hypoglycemia as monotherapy Added CV mortality and CV outcomes benefit in patients with known CVD
Sodium-glucose linked transporter 2 (SGLT2) Inhibitor	Enhances urinary glucose excretion by inhibiting glucose reabsorption in the proximal renal tubule	canagliflozin dapagliflozin empagliflozin	Invokana® Forxiga® Jardiance®		100-300 mg once daily before first meal of the day 5-10 mg once daily in the morning with or without food 10-25 mg once daily in the morning with or without food		ABSOLUTE: Severe renal impairment ESRD Patients on dialysis	UTI, genital infections Hypotension caution with concomitant loop diuretic use Caution with renal dysfunction Hyperlipidemia (raises LDL and HDL) Dapagliflozin not to be used in patients with active or history of bladder cancer Rare DKA (may occur with no hyperglycemia)	↓ A1c 0.7-1.0% Negligible risk of hypoglycemia as monotherapy Cause weight loss Added CV mortality, CV outcomes benefit in patients with known prior CVD Renal protection

Dyslipidemia Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
HMG-CoA Reductase Inhibitor (statins)	Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL	atorvastatin fluvastatin lovastatin pravastatin rosuvastatin simvastatin	Lipitor® Lescol® Mevacor® Pravachol® Crestor® Zocor®		10-80 mg/d 20-80 mg/d 20-80 mg/d 10-40 mg/d 5-40 mg/d 10-80 mg/d	1st line monotherapy Used for ↑ LDL, ↑ TG	Active liver disease	↑ liver enzymes Myositis (↑ risk if combined with fibrates) Rhabdomyolysis
Fibrates	Activate PPAR α, upregulate lipoprotein lipase + apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL	bezafibrate fenofibrate gemfibrozil	Bezalip® Lipidil® Lopid®		400 mg/d 48-200 mg/d 600-1200 mg/d	Used for ↑ TG, hyperchylomicronemia	Hepatic disease Renal disease	GI upset Skin rashes ↑ risk of gallstone formation ↑ risk of rhabdomyolysis when combined with statins
Niacin	Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL; decreased clearance of HDL	nicotinic acid	Niaspan® generic niacin	Niacor®	0.5-2 g/d	Used for severe hypertriglyceridemia not controlled by fibrate	Hypersensitivity Hepatic dysfunction Active peptic ulcer disease (PUD) Hyperuricemia Severe hypotension	Generalized flushing Abnormal liver enzymes Pruritus IGT Watch glucose control with overt DM
Bile Acid Sequestrants	Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL	cholestyramine colestipol	Questran® Colestid®		2-24 g/d 5-30 g/d	Used for ↑ LDL Use as adjunct with statins or fibrates	Complete biliary obstruction TG >3.5 mmol/L	Constipation, nausea Flatulence Bloating Rise in TG Binds other medications
Cholesterol Absorption Inhibitors	Inhibits cholesterol absorption at the small intestine brush border	ezetimibe	Ezetrol®	Zetia®	10 mg/d	Used for ↑ LDL	Hypersensitivity Hepatic dysfunction (when used with statin) Do not combine with fibrates or bile acid resins	Fatigue Pharyngitis Sinusitis Abdominal pain Diarrhea Arthralgia

Dyslipidemia Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Anti-PCSK9	Inhibits degradation of the LDL receptor by PCSK9 enzyme LDL clearance	evolocumab alirocumab	Repatha® Praluent®		140 mg q2 wk or 420 mg once monthly 75 mg q2 wk or 300 mg once monthly	Add-on to maximally tolerated statin therapy in heterozygous familial hypercholesterolemia (FH) (evolocumab, alirocumab) and homozygous FH (evolocumab) Consider in patients with atherosclerotic CVD and LDL-C not at target despite maximally tolerated statin ± ezetimibe	Hypersensitivity No studies regarding use in severe hepatic or renal impairment	Nasopharyngitis, URTI, influenza Sinusitis Back pain Myalgia Arthralgia Nausea

Thyroid Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Antithyroid Agent (thionamides)	Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T_4 and T_3 PTU also interferes with conversion of T_4 to T_3	propylthiouracil (PTU) methimazole (MMI)	Propyl-Thyracil® Tapazole®		Start 100 mg PO TID, then adjust accordingly Thyroid storm: start 150-300 PO QID, then adjust accordingly Start 5-20 mg PO once daily, then adjust accordingly Up to 60 mg once daily may be required	Hyperthyroidism, thyroid storm	Hypersensitivity PTU recommended in 1st trimester, MMI during 2nd and 3rd trimester Lactation: safe with PTU <300 mg/d and MMI <20-30 mg/d	N/V Rash Drug-induced hepatitis Agranulocytosis Hepatitis with PTU Cholestasis with MMI Vasculitis
Thyroid Hormone	Synthetic form of thyroxine (T_4)	levothyroxine l-thyroxine	Synthroid® Eltroxin®	Levoxyl®	0.05-2.0 mg/d, usually 1.6x weight (kg) is dose in micrograms In elderly patients start at 0.025 mg/d	Hypothyroidism Post thyroidectomy	Recent MI, thyrotoxicosis	If wrong dosing: symptoms of hypothyroidism or hyperthyroidism Skin rash from dye in pill
Antithyroid Agent Radiopharmaceutical	Radioactive isotope of iodine that is incorporated into the thyroid gland irradiating the area and destroying local glandular tissue	sodium iodide I-131	Iodotope®		Dose corrected for 24 h radioactive iodine uptake Hyperthyroidism 4-12 millicuries (mCi) Thyroid Ca 50-150 mCi	Hyperthyroidism Thyroid malignancy	Hypersensitivity Concurrent antithyroid medication Pregnancy, lactation	N/V Bone marrow suppression Sialadenitis Thyroiditis

Metabolic Bone Disease Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Bisphosphonates	Inhibits osteoclast-mediated bone resorption	alendronate	Fosamax®		Osteoporosis: 5-10 mg once daily 70 mg once weekly Paget's: 40 mg once daily for 6 mo	Treaatment of postmenopausal osteoporosis Treatment of osteoporosis Glucocorticoid-induced osteoporosis Paget's disease	Esophageal stricture or achalasia (oral) Unable to stand or sit upright for >30 min (oral) Hypersensitivity Hypocalcemia Renal insufficiency (CrCl <35 mL/min) History or atypical femoral fracture or osteonecrosis of the jaw	GI Musculoskeletal (MSK) pain Headache Osteonecrosis of the jaw Atypical femur fractures
		risedronate	Actonel®		Osteoporosis: 5 mg once daily 35 mg once weekly 150 mg once monthly Paget's: 30 mg once daily for 2 mo	Treatment of postmenopausal osteoporosis Treatment and prevention of glucocorticoid-induced osteoporosis Paget's disease	Same as above	Same as above
		pamidronate	Aredia®		Hypercalcemia of malignancy: 60-90 mg IV over 2-24 h Wait at least 7 d before considering retreatment	Hypercalcemia of malignancy Paget's disease Osteolytic bone metastases of breast cancer Osteolytic lesions of multiple myeloma	Renal insufficiency (CrCl <30 mL/min)	
		zoledronate	Zometa® Aclasta®	Reclast®	5 mg IV once yearly 5 mg IV	Treatment of osteoporosis Hypercalcemia of malignancy Treatment and prevention of skeletal complications related to cancer	Renal insufficiency (CrCl <35 mL/min)	
Selective Estrogen Receptor Modulators	Decreases resorption of bone through binding to estrogen receptors	raloxifene	Evista®		60 mg once daily	Treatment and prevention of postmenopausal osteoporosis (2nd line)	Lactation Pregnancy Active or past history of DVT, PE, or retinal vein thrombosis	Hot flashes Leg cramps Increased risk of fatal stroke, venous thromboembolism
Anti-RANKL Monoclonal Ab	Inhibits RANKL (osteoclast differentiating factor) → inhibits osteoclast formation and decreases bone resorption	denosumab	Prolia™		60 mg SC q6 mo	Treatment for postmenopausal women at high-risk of fracture Prevent skeletal-related events in patients with bone metastasis from solid tumours Also approved for glucocorticoid-induced osteoporosis, and for men	Hypocalcemia Vitamin D insufficiency	Fatigue/headache/GI injection site reaction Hypocalcemia Atypical femur fractures Osteonecrosis of the jaw
PTH analog	Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity	teriparatide	Forteo® and Osnuvo®		20 µg SC once daily x 18-24 mo	Treatment for postmenopausal women with osteoporosis who are at high-risk for fracture Treatment for men with primary or hypogonadal osteoporosis who are at high-risk for fracture Also approved for glucocorticoid-induced osteoporosis	Paget's disease Prior external beam or implant radiation therapy involving the skeleton Bone metastases Metabolic bone diseases other than osteoporosis	Orthostatic hypotension Hypercalcemia Dizziness Leg cramps
Calcium	Inhibits PTH secretion				1200 mg/d (including diet) Divided in 3 doses	Osteopenia Osteoporosis Prevention of metabolic bone disease	Caution with renal stones	Vomiting Constipation Dry mouth
Anti-sclerostin Monoclonal Ab	Binds to and inhibits sclerostin (inhibitor of Wnt β-Catenin pathway) → increased bone formation and reduced bone resorption	Romosozumab	Evenity®		210 mg SC qMonth x 12 mo	Treatment of osteoporosis in postmenopausal women at high risk for fracture (defined as history of osteoporotic fracture or multiple risk factors for fracture)	Hypocalcemia Hypersensitivity	Headache, joint pain, pain at injection site May increase risk of MI/stroke/CV death Osteonecrosis of jaw Atypical femur fractures

Metabolic Bone Disease Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Vitamin D	Regulation of calcium and phosphate homeostasis	cholecalciferol (vitamin D_3)			800 -2000 IU/d (higher doses required in Insufficiency or deficiency)	Osteopenia Osteoporosis Prevention of metabolic bone disease	Caution in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia)	Hypercalcemia Headache N/V Constipation
		ergocalciferol (vitamin D_2)	Drisdol® Erdol®		50000 IU/wk	Osteoporosis in patients with liver dysfunction, refractory rickets, hypoparathyroidism	Hypercalcemia Malabsorption syndrome Decreased renal function	
		calcitriol ($1,25(OH)_2$-D)	Rocaltrol®		Start 0.25 µg/d Titrate up by 0.25 µg/d at 4-8 wk intervals to 0.5-1 µg/d	Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis Hypoparathyroidism	Hypercalcemia Vitamin D toxicity	
			Calcijex®		Start 0.25 µg/d Titrate up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d			

Adrenal Medications

Drug Class	Mineralocorticoid Activity	Generic Drug Name	Potency Relative to Cortisol	Equivalent Dose (mg)	Duration of Action (t1/2 in h)	Dosing	Comments
Glucocorticoid	Yes	Hydrocortisone (cortef, solu-Cortef)	1.0	20	8	Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q8 h (continuous infusion x 24-48 h) PO once stable (50 mg q8 h x 48 h, then taper over 14 d) Chronic AI: 15-20 mg PO BID-TID (2/3 AM, 1/3 PM)	In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low K^+ metabolic alkalosis)
Glucocorticoid	Yes	cortisone acetate	0.8	25	oral = 8 IM = 18+	Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24 h Chronic AI: 25 mg/d divided BID-TID	Pro-drug which is converted to active form as hydrocortisone High doses can result in mineralocorticoid side effects (see above)
Glucocorticoid	Yes	prednisone	4	5	16-36	Adrenal Crisis:Adrenal Crisis: 15-60 mg/d PO once daily or divided BID/OID Chronic AI: 5 mg daily	Pro-drug which is converted to active form as prednisolone
Glucocorticoid	No	dexamethasone	30	0.75	36-54	Adrenal Crisis: 4 mg IV; repeat q2-6 h if necessary	
Mineralocorticoid	100%	Fludrocortisone (florinef acetate)	—			Chronic: 0.1 mg daily	Replaces aldosterone in primary adrenal insufficiency

Landmark Endocrinology Trials

Trial Name	Reference	Clinical Trial Details
Diabetes Prevention		
DPP Research Group: Lifestyle	NEJM 2002;346:393-403	**Title**: Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin **Purpose**: To investigate whether lifestyle interventions or metformin could prevent or delay the development of T2DM. **Methods**: 3234 nondiabetic persons with elevated fasting and post-load plasma glucose were randomly assigned to placebo, metformin (850 mg BID), or a lifestyle-modification program (min 7% weight loss and 150 min of physical activity/wk). **Results**: Lifestyle interventions and metformin reduced the incidence of T2DM by 58% (95% confidence interval [CI], 48-66%) and 31% (CI, 17-43%), respectively, as compared with placebo. Lifestyle interventions were significantly more effective than metformin. **Conclusion**: Metformin and lifestyle modifications reduced the incidence of diabetes in high-risk individuals but lifestyle modifications were more effective.
Look AHEAD	NEJM 2013;369:145-54	**Title:** Title: Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes Purpose: To investigate if an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among overweight or obese patients with T2DM. **Methods:** 5145 patients were randomly assigned to receive weight loss lifestyle interventions (decreased caloric intake and increased physical activity) or diabetes support and education (control). **Results**: Trial was stopped early on the basis of futility. As compared to control, lifestyle interventions reduced weight, HbA1c and cardiovascular risk factors, but the incidence of the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina) was not significantly different between the groups. **Conclusion**: Rate of cardiovascular events in overweight or obese adults with T2DM were not reduced by an intensive lifestyle intervention focusing on weight loss
A1c Targets		
ADVANCE	NEJM 2008;358:2560-72	**Title:** Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes **Purpose:** To investigate the effects of intensive glucose control on vascular outcomes in patients with T2DM. **Methods:** 11140 patients with T2DM received intensive glucose control with modified release gliclazide (and other drugs necessary to reach target HbA1c ≤6.5%) or standard glucose control (target HbA1c defined by local guidelines). **Results:** Intensive glucose control reduced the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% confidence interval [CI], 0.66-0.93; P=0.006), but did not significantly reduce major macrovascular events or death from any cause. Severe hypoglycemia was more common in the intensive control group (2.7%, vs. 1.5%; 1.86 CI [1.42 to 2.40]; P<0.001). **Conclusion:** Intensive glucose control targeting HbA1c ≤6.5% significantly reduces the incidence of nephropathy but not major macrovascular events or death.
ACCORD	NEJM 2008;358:2545-59	**Title:** Effects of Intensive Glucose Lowering in Type 2 Diabetes **Purpose:** To investigate if intensive glucose control targeting normal HbA1c levels reduces cardiovascular events in patients with T2DM with established CVD or CVD risk factors. **Methods:** 10251 patients (mean age 62.2) were randomly assigned to receive intensive therapy targeting a HbA1c level of <6.0% or standard therapy targeting 7.0-7.9%. **Results:** The intensive therapy arm was stopped early due to evidence of increased mortality. There was no difference in cardiovascular events or death from cardiovascular events. There were increased rates of hypoglycemia, fluid retention, and weight gain >10 kg in the intensive therapy group. **Conclusion:** Intensive glucose lowering therapy in T2DM does not improve clinical outcomes and increases mortality with more adverse events.
VADT	NEJM 2009;129-39	**Title:** Glucose Control And Vascular Complications In Veterans With Type 2 Diabetes **Purpose:** To investigate effects of intensive glucose control on cardiovascular events in patients with long-standing T2DM. **Methods:** 1791 military veterans who had suboptimal responses to therapy for T2DM were randomly assigned to intensive control (absolute reduction in HbA1c by 1.5% relative to standard) or standard glucose control. **Results:** Median HbA1c was 6.9% in the intensive-therapy group and 8.4% in the standard-therapy. Risk of major cardiovascular events, microvascular complications, or death from any cause were not significantly different between groups. Adverse events, predominantly hypoglycemia, were more common in the intensive control group. **Conclusion:** Rates of major cardiovascular events, death, or microvascular complications were not reduced by intensive glucose control in patients with poorly controlled T2DM.
Diabetes Treatment		
4T Trial	NEJM 2009;361:1736-1747	**Title:** Three Year Efficacy of Complex Insulin Regimens in T2DM: 4T Trial Study: Randomized Unblinded Trial with 3 yr of Follow-up **Population**: 708 patients with T2DM, not on insulin or thiazolidinedione therapy on maximal metformin and sulfonylurea therapy. **Intervention**: Thrice-daily prandial insulin aspart, vs. twice-daily biphasic insulin aspart, vs. once-daily basal insulin detemir. Sulfonylurea therapy was replaced with a secondary insulin regime specific to each arm if there was persistent hyperglycemia. **Primary Outcome**: Three yr HbA1c. **Results**: Significant difference in rates of patient withdrawal from the study: 5.1% biphasic, 11.7% prandial, 8.5% basal regimens (P=0.04). There were no significant differences in median HbA1c levels between all three arms from yr 1-3. A smaller proportion of patients reached HbA1c <6.5% or <7.0% in the biphasic arm. The basal arm had the least weight gain and the least weight circumference increase, but the highest rate of secondary insulin requirement. The basal arm had fewest severe hypoglycemic events per patient year, while the biphasic had the most serious adverse effects. **Conclusion**: Basal insulin regimen provides the best glycemic control over a 3 yr study, with better HbA1c control, fewer hypoglycemic events, and less weight gain.
The ACCORD Trial – Blood Pressure Control	NEJM 2010;362:1575-1585	**Title:** Effects of Intensive Blood Pressure Control in T2DM: The ACCORD Trial **Study**: RCT, unblinded with 4.7 yr of mean follow-up. **Population**: 4733 patients with T2DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg. **Intervention**: sBP control <120 mmHg (intensive) or 140 mmHg (standard). **Primary Outcomes**: Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death). **Results**: Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI 3.4-3.5) vs. 2.1 (95% CI 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.27%, P≤0.001); especially bradycardia or arrhythmia (0.5% vs. 0.13%, P=0.02) and hyperkalemia (0.4% vs. 0.04%, P=0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32%/yr vs. 0.53%/yr, P=0.01) and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, P=0.03) in the intensive therapy arm. **Conclusion**: Intensive BP lowering to <120 mmHg vs. 140 mmHg in patients with T2DM and CV risk factors does not reduce major CV event risk except for stroke events.

Trial Name	Reference	Clinical Trial Details
The ACCORD Trial – Combination Lipid Therapy	NEJM 2010;362:1563-1574	**Title:** Effects of Combination Lipid Therapy in T2DM: The ACCORD Trial **Study**: RCT, double-blinded trial with 4.7 yr of mean follow-up. **Population**: 5518 patients with T2DM. Intervention: Statin with or without fibrate therapy. Primary Outcome: Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death). **Results**: No significant differences in primary outcome between the two arms. No difference in all MI, all stroke, or all-cause mortality between study arms. **Conclusions**: The addition of fibrate therapy to statin therapy in patients with T2DM does not reduce major CV event risk.
DCCT	NEJM 1993;329:977-986	**Title:** The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-term Complications in Insulin-dependent Diabetes Mellitus **Purpose:** To investigate whether intensive treatment to maintain normal blood glucose reduces the frequency and severity of microvascular complications in T1DM. **Methods:** 1441 patients with T1DM received intensive therapy (≥3 daily insulin injections or insulin pump, BG monitoring QID with strict targets) or conventional therapy (1-2 insulin injections daily, BG monitoring daily). **Results:** Intensive treatment of T1DM significantly reduced the risk for the development and progression of retinopathy in primary- and secondary-intervention cohorts, respectively. Intensive therapy also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy. Intensive therapy was associated with an increase in the occurrence of severe hypoglycemia. **Conclusion:** Intensive treatment significantly reduces the development and progression of microvascular complications in T1DM.
EDIC	NEJM 2005;353:2644-53	**Title:** Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes **Purpose:** To investigate whether intensive vs. conventional therapy during the DCCT trial influenced the long-term incidence of CVD. **Methods:** The DCCT trial randomly assigned 1441 patients with T1DM to intensive or conventional therapy for a mean of 6.5 years from 1983-1993. 93% were followed until 2005 (EDIC) for cardiovascular events. **Results:** During the mean 17-year follow-up, intensive treatment reduced the risk of any cardiovascular event by 42% (95% confidence interval (CI), 9-63%; P=0.02) and of nonfatal MI, stroke, or death from CVD by 57% (CI, 12-79%; P=0.02). **Conclusion:** Long-term risk of CVD in patients with T1DM is reduced by intensive therapy.
UKPDS 33	Lancet 1998;352:837-53	**Title:** Intensive Blood-Glucose Control With Sulphonylureas or Insulin Compared With Conventional Treatment and Risk of Complications In Patients With Type 2 Diabetes (UKPDS 33) **Purpose:** To investigate the effects of intensive blood-glucose control with sulphonylurea or insulin vs. conventional treatment on the risk of complications in T2DM. **Methods:** 3867 patients with newly diagnosed T2DM received intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <15 mmol/L without hyperglycemic symptoms). **Results:** Patients allocated to intensive treatment had lower median HbA1c levels (P<0.0001), and their risk was reduced by 12% for any diabetes-related endpoint (95% confidence interval [CI], 1-21, P=0.029), by 10% for any diabetes-related death (CI, -11-27, P=0.34), and by 6% for all-cause mortality (CI, -10-20, P=0.44). Intensive therapy induced more hypoglycemic episodes and weight gain. **Conclusion:** In T2DM, sulphonylurea or insulin-mediated intensive glucose control reduced microvascular but not macrovascular complications.
UKPDS 34	Lancet 1998;352:854-65	**Title:** Effect of Intensive Blood-Glucose Control With Metformin On Complications In Overweight Patients With Type 2 Diabetes (UKPDS 34) **Purpose:** To investigate the effects of intensive glucose control with metformin on rates of microvascular and macrovascular complications in overweight patients with T2DM. **Methods:** 753 patients were randomized to receive conventional management with diet alone or intensive blood-glucose control regimen with metformin targeting FPG<6 mmol/L. **Results:** Patients allocated metformin had reduced HbA1c (7.4% vs. 8.0%), and risk reductions of 32% for any diabetes-related endpoint (P=0.002), 42% for diabetes-related death (P=0.017), and 36% for all-cause mortality (P=0.011). Among various intensive blood-glucose control regimens, metformin was superior to sulphonylureas or insulin for any diabetes-related endpoint (P=0.0034), all-cause mortality (P=0.021), and stroke (P=0.032). **Discussion:** Metformin decreases risk of diabetes-related endpoints in overweight patients with less weight gain and hypoglycemia than insulin and sulphonylureas. Consider for first line therapy.
UKPDS Extension	NEJM 2008;359:1577-89	**Title:** 10-Year Follow-Up of Intensive Glucose Control in Type 2 Diabetes **Purpose:** Post-trial monitoring of UKPDS to determine whether improved glucose control persisted and if there were long-term effects on macrovascular outcomes. **Methods:** 3277 patients were assessed through annual UKPDS clinics or annual questionnaires for up to 10 yr. **Results:** After 1 yr, between-group differences in HbA1c were lost. Relative risk reductions in the sulfonylurea-insulin group persisted for any diabetes-related end point (9%, P=0.04) and microvascular disease (24%, P=0.001), in addition to the emergence of risk reductions for MI (15%, P=0.01) and death from any cause (13%, P=0.007). Risk reductions persisted in the metformin group for any diabetes-related end point (21%, P=0.01), MI (33%, P=0.005), and death from any cause (27%, P=0.002). **Conclusion:** Glycemic differences were lost early, but sustained reductions in microvascular risk and emergent risk reductions for MI and death were evident during 10 years of post-trial follow-up.
Steno-2	NEJM 2008;358:580-91	**Title**: Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes **Purpose**: To investigate if intensified multifactorial interventions would influence rates of death in patients with T2DM and microalbuminuria. **Methods**: 160 patients received either conventional multifactorial treatment or intensified, target-driven therapy involving a combination of medications and focused behaviour modification. **Results**: A lower risk of death from any cause, death from cardiovascular causes, cardiovascular events, and progression to end-stage renal disease was seen in intensive therapy, and fewer patients in this group required retinal photocoagulation. **Conclusion**: Vascular complications and death rates were significantly improved by multifactorial interventions in at-risk patients with T2DM.

Trial Name	Reference	Clinical Trial Details
LIPIDS		
IMPROVE-IT	NEJM 2015;372:2387-97	**Title:** Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes **Purpose:** To assess whether the addition of ezetimibe to statin therapy can further reduce the rate of cardiovascular events. **Methods:** 18144 patients who had been hospitalized within the previous 10 d for acute coronary syndrome (ACS) with LDL cholesterol = 1.3 to 2.6 mmol/L (if on lipid lowering therapy) or 1.3 to 3.2 mmol/L (if not on lipid lowering therapy) were randomly assigned to receive a combination of either simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin-ezetimibe) or simvastatin (40 mg) and placebo (monotherapy). **Results:** Median time-weighted average LDL cholesterol was significantly lower in the simvastatin-ezetimibe group as compared to monotherapy (1.4 vs. 1.8 mmol/L; P<0.001). At 7 yr, the simvastatin-ezetimibe group was associated with significantly lower Kaplan-Meier event rates of the primary composite outcome (cardiovascular death, nonfatal MI, unstable angina, coronary revascularization, or nonfatal stroke) (32.7% vs. 34.7%; hazard ratio, 0.936; 95% CI, 0.89-0.99; P=0.016). **Conclusion:** Ezetimibe, when added to statin therapy, resulted in lower LDL cholesterol and improved cardiovascular outcomes. Additional benefit was conferred by lowering LDL cholesterol below previous targets.
FOURIER	NEJM 2017;376:1713-22	**Title:** Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease **Purpose:** To assess if the PCSK9 inhibitor evolocumab prevents cardiovascular events. **Methods:** 27564 patients with atherosclerotic CVD and LDL cholesterol ≥1.8 mmol/L who were on statin therapy were randomly assigned to receive evolocumab (140 mg every 2 wk or 420 mg monthly) or matching placebo. **Results:** At 48 wk, evolocumab was associated with a least-squares mean percentage reduction in LDL cholesterol of 59% relative to placebo, from a median baseline of 2.4 mmol/L to 0.78 mmol/L (P<0.001). Patients in the evolocumab group experienced significantly lower rates of the primary composite outcome (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) as compared to placebo (9.8% vs. 11.3%, respectively; hazard ratio, 0.85; 95% CI, 0.79-0.92; P<0.001). **Conclusion:** Evolocumab lowers LDL cholesterol and reduces the risk of cardiovascular events in patients with atherosclerotic CVD.
ODYSSEY OUTCOMES	NEJM 2018;379:2097-107	**Title:** Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome **Purpose:** To determine if the PCSK9 inhibitor alirocumab improves cardiovascular outcomes following acute coronary syndromes (ACS) in patients on high-intensity statin therapy. **Methods:** 18924 patients on high-intensity statin therapy who experienced ACS 1-12 mo prior with LDL cholesterol ≥ 1.8 mmol/L and non-HDL-C ≥ 2.6 mmol/L or ApoB ≥ 80 mg/dL were randomly assigned to receive SC alirocumab (75 mg) or matching placebo every two wk. **Results:** At median follow-up of 2.8 mo, the composite primary outcome (death from coronary heart disease, non-fatal MI, ischemic stroke, or hospitalization for unstable angina) occurred in 9.5% and 11.1% of patients on alirocumab and placebo, respectively (hazard ratio, 0.85; 95% CI 0.78-0.93; P<0.001). Alirocumab was associated with greater absolute benefit with respect to the primary outcome in patients with higher baseline LDL cholesterol. **Conclusion:** Alirocumab reduces the risk of recurrent ischemic cardiovascular events in patients who had a previous ACS on high-intensity statin therapy.
REDUCE-IT	NEJM 2019;380:11-22	**Title:** Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia **Purpose:** To assess the effects of icosapent ethyl on the rate of ischemic events. **Methods:** 8179 patients with established CVD or diabetes and other risk factors, who were on statin therapy with fasting TG 1.52-5.63 mmol/L and LDL cholesterol 1.06-2.59 mmol/L were randomly assigned to receive icosapent ethyl (2 g BID) or placebo. **Results:** At median follow-up of 4.9 yr, the primary composite end point (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) occurred in significantly less patients in the icosapent ethyl group as compared to placebo (17.2% vs. 22.0%, respectively; hazard ratio, 0.75; 95% CI, 0.68-0.83; P<0.001). Icosapent ethyl was associated with significantly higher rates of hospitalization for atrial fibrillation or flutter as compared to placebo (3.1% vs. 2.1%; P=0.004). **Conclusion:** Icosapent ethyl therapy was associated with a significantly lower risk of ischemic events in patients with elevated TGs despite the use of statins.
4S	Lancet 1994;344:1383-1389	**Title:** Randomised Trial of Cholesterol Lowering In 4444 Patients With Coronary Heart Disease: The Scandinavian Simvastatin Survival Study (4S) **Purpose:** To investigate if cholesterol lowering with simvastatin alters mortality and morbidity in patients with coronary heart disease (CHD). **Methods:** 4444 patients with CHD and serum cholesterol 5.5-8.0 mmol/L on a lipid-lowering diet received simvastatin or placebo. **Results:** In the simvastatin group, mean changes in total cholesterol, LDL, and HDL of -25%, -35%, and +8%, respectively, were observed with few adverse effects. The relative risk of coronary events in the simvastatin group was 0.66 (95% confidence interval [CI], 0.59-0.75, P<0.00001) and relative risk of death was 0.70 (CI, 0.58-0.85, P=0.0003). **Conclusion:** In CHD patients, long-term treatment with simvastatin safely improves survival.
HPS	Lancet 2002;360:7-22	**Title:** MRC/BHF Heart Protection Study Of Cholesterol Lowering With Simvastatin In 20536 High-Risk Individuals: A Randomised Placebo-Controlled Trial **Purpose:** To investigate the effects of reducing LDL cholesterol on the development of vascular disease. **Methods:** 20536 adults with coronary disease, other occlusive arterial disease, or diabetes received 40 mg simvastatin daily or placebo. **Results:** As compared to placebo, simvastatin significantly reduced all-cause mortality (12.9% vs.14.7%; P=0.0003), mainly due to an 18% reduction in the coronary death rate (5.7% vs. 6.9%; P=0.0005). There were significant reductions in the first event rate for non-fatal MI or coronary death (8.7% vs. 11.8%; P<0.0001), for non-fatal or fatal stroke (4.3% vs. 5.7%; P<0.0001), and for coronary or non-coronary revascularisation (9.1% vs. 11.7%; P<0.0001). **Conclusion:** Adding simvastatin treatment safely protects against vascular disease in a variety of high-risk patients.
FIELD	Lancet 2005;366:1849-61	**Title:** Effects of Long-Term Fenofibrate Therapy on Cardiovascular Events In 9795 People With Type 2 Diabetes Mellitus (The FIELD Study): Randomised Controlled Trial **Purpose:** To assess the effect of fenofibrate on cardiovascular events in patients with T2DM at high risk for CVD. **Methods:** 9795 patients with T2DM not taking statin therapy were randomly assigned to micronized fenofibrate 200 mg daily or placebo. **Results:** Fenofibrate significantly reduced the relative risk of non-fatal MI (hazard ratio [HR], 0.76, 95% confidence interval [CI], 0.62-0.94; P=0.010) and total cardiovascular events (HR, 0.89; CI, 0.80-0.99; P=0.035), but there was no significant difference in the risk of coronary events or CHD mortality between groups. **Conclusion:** Fenofibrate did not significantly reduce the risk of coronary events, but rates of total cardiovascular events (mainly non-fatal MIs and revascularizations) were reduced.

Trial Name	Reference	Clinical Trial Details
TNT	NEJM 2005;352:1425-35	**Title:** Intensive Lipid Lowering With Atorvastatin In Patients With Stable Coronary Disease **Purpose:** To assess the efficacy and safety of reducing LDL to <2.6 mmol/L in patients with stable coronary heart disease (CHD). **Methods:** 10001 patients with CHD and LDL<3.4 mmol/L were randomly assigned to receive either 10 mg or 80 mg of atorvastatin daily. **Results:** Mean LDL was 2.0 mmol/L and 2.6 mmol/L during treatment with 80 mg and 10 mg of atorvastatin, respectively. Major cardiovascular events occurred in 8.7% receiving 80 mg vs. 10.9% receiving 10 mg, indicating a 22% relative risk reduction (hazard ratio, 0.78; 95% confidence interval, 0.69-0.89; P<0.001). **Conclusion:** In patients with stable CHD, intensive lipid-lowering treatment with 80 mg atorvastatin daily has greater clinical efficacy than 10 mg of atorvastatin daily.
Jupiter	NEJM 2008;359:2195-207	**Title:** Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein **Purpose:** To investigate if statins reduce cardiovascular events in patients with elevated CRP but without hyperlipidemia. **Methods:** 17802 healthy men and women with LDL<130 mg/dL and CRP>2.0 mg/L were randomly assigned to receive rosuvastatin 20 mg daily or placebo. **Results:** Rosuvastatin reduced LDL and CRP levels by 50% and 37%, respectively. In the rosuvastatin and placebo groups, the rates of the primary outcomes (MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CVD) were 0.77 and 1.36 per 100 person-years of follow-up, respectively (P<0.00001). **Conclusion:** Statins reduce the incidence of major cardiovascular events in healthy people without hyperlipidemia but with an elevated CRP.
SGLT2 Inhibitors - Renal		
CREDENCE	NEJM 2019;380:2295-2306	**Title:** Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy **Purpose:** To investigate if an SGLT2i improves renal outcomes in patients with T2DM. **Methods:** 4401 patients with T2DM and chronic kidney disease (CKD) were randomly assigned to receive either 100 mg canagliflozin (oral SGLT2i) daily or placebo. **Results:** Trial was stopped early after median follow-up of 2.6 yr. Canagliflozin significantly lowered the relative risk of the primary composite outcome (end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes) by 30% (hazard ratio, 0.70; 95% confidence interval, 0.59-0.82; P=0.00001). **Conclusion:** Canagliflozin therapy resulted in a lower risk of kidney failure and cardiovascular events in patients with T2DM and CKD.
DAPA-CKD	NEJM 2020;383:1436-46	**Title:** Dapagliflozin in Patients with Chronic Kidney Disease **Purpose:** To assess the effects of SGLT2is in patients with CKD with or without T2DM. **Methods:** 4304 patients with estimated GFR (eGFR) = 25 to 75 mL/min/1.73m^2 and urinary ACR = 200 to 5000 were randomly assigned to receive dapagliflozin (10 mg/d) or placebo. **Results:** Over a median of 2.4 yr, dapagliflozin was associated with significantly lower rates of the primary composite outcome (sustained decline in eGFR ≥50%, end-stage kidney disease, or death from renal or cardiovascular outcomes) as compared to placebo (9.2% vs. 14.5%; hazard ratio, 0.61; 95% CI, 0.51-0.72; P<0.001). Effects were similar in patients with and without T2DM. **Conclusion:** Dapagliflozin therapy resulted in a lower risk of kidney failure and cardiovascular events in patients with CDK, with or without T2DM.
EMPA-KIDNEY	NEJM 2023; 388:117-127	**Title:** Empagliflozin in Patients with Chronic Kidney Disease **Purpose**: To understand empagliflozin's effects on at-risk chronic kidney disease patients. **Methods**: Patients with chronic kidney disease were enrolled based on specific eGFR and urinary albumin-to-creatinine ratio criteria. They were randomly assigned to receive empagliflozin or placebo to evaluate kidney disease progression and cardiovascular-related mortalit. **Results**: Among 6609 patients enrolled, empagliflozin demonstrated benefits in chronic kidney disease. Compared to the placebo group, the empagliflozin group had a lower incidence of kidney disease progression or cardiovascular death (13.1% vs. 16.9%). Similar results were observed across diabetes status and eGFR ranges, with no significant differences in adverse events. Conclusion: Empagliflozin therapy showed lower risk of kidney disease progression or cardiovascular death compared to placebo in at-risk patients with chronic kidney disease.
Additional Trials: see Landmark Clinical Trials C74		
LEADER (GLP-1 Agonists)	NEJM 2016;375:311-22	**Title**: Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
REWIND (GLP-1 Agonists)	Lancet 2019;394:121-30	**Title**: Dulaglutide and Cardiovascular Outcomes in T2DM (REWIND): A Double-Blind, Randomized Placebo-Controlled Trial
AMPLITUDE-O (GLP-1 Agonists)	NEJM 2021; 385: 896-907	**Title**: Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes
HARMONY-OUTCOMES (GLP-1 Agonists)	Lancet 2018; 392: 1519-1529	**Title**: Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomized placebo-controlled trial
SUSTAIN-6 (GLP-1 Agonists)	NEJM 2016; 375: 1834-1844	**Title**: Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
PIONEER 6 (GLP-1 Agonists)	NEJM 2019; 381: 841-851	**Title**: Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
EMPA-REG OUTCOME (SGLT2 Inhibitors)	NEJM 2015;373:2117-28	**Title**: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
CANVAS (SGLT2 Inhibitors)	NEJM 2017;377:644-57	**Title**: Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
DECLARE-TIMI 58 (SGLT2 Inhibitors)	NEJM 2019;380:347-57	**Title**: Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes
DAPA-HF (SGLT2 Inhibitors)	NEJM 2019;381:1995-2008	**Title**: Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction
DELIVER (SGLT2 Inhibitors)	NEJM 2022; 387:1089-1098	**Title**: Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction
EMPEROR-Preserved (SGLT2 Inhibitors)	NEJM 2021;385:1451-1461	**Title**: Empagliflozin in Heart Failure with a Preserved Ejection Fraction
EMPEROR-Reduced (SGLT2 Inhibitors)	NEJM 2020;383:1413-24	**Title**: Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure
PRESERVED-HF (SGLT2 Inhibitors)	Nature 2021; 27: 1954-1960	**Title**: The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial

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FM Family Medicine

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Acronyms

ABG	arterial blood gas
ACR	albumin:creatinine ratio
ACEI	angiotensin converting enzyme inhibitors
AIN	anal intraepithelial neoplasia
AKI	acute kidney injury
AMC	another medical condition
AR	absolute risk
ARB	angiotensin receptor blocker
BPH	benign prostatic hyperplasia
BPPV	benign paroxysmal positional vertigo
BRBPR	bright red blood per rectum
CA	cancer
CABG	coronary artery bypass graft
CAM	complementary and alternative medicine
CANRISK	Canadian Diabetes Risk Questionnaire
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CCS	Canadian Cancer Society
CF	cystic fibrosis
CHEP	Canadian Hypertension Education Program
CK	creatine kinase
CNS	central nervous system
CPAP	continuous positive airway pressure
CRC	colorectal cancer
CrCl	creatinine clearance
CRP	C-reactive protein
CSEP	Canadian Society for Exercise Physiology
CV	cardiovascular
CVA	costovertebral angle
CVD	cardiovascular disease
DASH	dietary approaches to stop hypertension
DHP	dihydropyridine
DKA	diabetic ketoacidosis
DMPA	depot medroxyprogesterone
DRE	digital rectal exam
DS	double strength
EC	emergency contraception
ER	extended release
F/U	follow-up
FAP	familial adenomatous polyposis
FBG	fasting blood glucose
FHT	family health team
FIT	fecal immunochemical test
FOBT	fecal occult blood test
FP	family physician
FRS	Framingham risk score
GAD	generalized anxiety disorder
GERD	gastroesophageal reflux disease
GDS	geriatric depression scale
gFOBT	guaiac fecal occult blood test
GP	general practitioner
HAART	highly active anti-retroviral therapy
HDL	high density lipoprotein
HDL-C	high density lipoprotein cholesterol
HEENT	head, ears, eyes, nose, and throat
HF	heart failure
HNPCC	hereditary non-polyposis colon cancer
hs-CRP	high sensitivity C-reactive protein
HSIL	high-grade squamous intraepithelial lesion
HPV	human papillomavirus
HRT	hormone replacement therapy
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICS	inhaled corticosteroid
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IHD	ischemic heart disease
INH	isoniazid
IPT	interpersonal therapy
IUD	intrauterine device
IVP	intravenous pyelogram
KUB	kidney, ureter, bladder
LDCT	low dose computed tomography
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LMWH	low molecular weight heparin
LSIL	low-grade squamous intraepithelial lesion
LV	left ventricle
LVH	left ventricular hypertrophy
MCV	mean corpuscular volume
MMSE	mini mental status examination
MOCA	Montreal cognitive assessment
MS	multiple sclerosis
MSM	men who have sex with men
MUFA	monounsaturated fatty acids
NE	norepinephrine
NHP	natural health product
NNT	number-needed-to- treat
NNH	number-needed-to-harm
NP	nurse practitioner
NPH	neutral protamine hagedorn
NRT	nicotine replacement therapy
NTD	neural tube defect
NTG	nitroglycerin
NYHA	New York Health Association
O&P	ova and parasites
OA	osteoarthritis
OCD	obsessive compulsive disorder
OCP	oral contraceptive pill
OCPD	obsessive compulsive personality disorder
OD	omne in die (i.e. once daily)
OGTT	oral glucose tolerance test
OSA	obstructive sleep apnea
PCOS	polycystic ovarian syndrome
PCSK9	proprotein convertase subtilisin/kexin 9
PFT	pulmonary function test
PHE	periodic health examination
PHQ	patient health questionaire
PID	pelvic inflammatory disease
PMS	premenstrual syndrome
PND	paroxysmal nocturnal dyspnea
PPD	purified protein derivative
PSA	prostate specific antigen
PTSD	post-traumatic stress disorder
PUD	peptic ulcer disease
PUFA	polyunsaturated fatty acids
PVD	peripheral vascular disease
PVR	post-void residual
QHS	quaque hora somni (i.e. every night at bedtime)
R&M	routine and microscopic
RA	rheumatoid arthritis
RN	registered nurse
ROM	range of motion
RR	relative risk
RSV	respiratory syncytial virus
SAH	subarachnoid hemorrhage
SDRI	serotonin dopamine reuptake inhibitor
SIDS	sudden infant death syndrome
SNRI	serotonin norepinephrine reuptake inhibitor
SOB	shortness of breath
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
TC	total cholesterol
TCA	tricyclic antidepressant
TDEE	total daily energy expenditure
TG	triglyceride
TIA	transient ischemic attack
TM	tympanic membrane
TMJ	temporomandibular joint
TUIP	transurethral incision of the prostate
TURP	transurethral resection of the prostate
UC	ulcerative colitis
URTI	upper respiratory tract infection
VAIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
VBI	vertebrobasilar insufficiency
WC	waist circumference
WSIB	Workplace Safety and Insurance Board

Four Principles of Family Medicine

College of Family Physicians of Canada

1. the family physician is a skilled clinician
   - works with patients to understand their illness experience and collaborate on shared management plans
   - uses expert generalist knowledge to develop a comprehensive approach to the management of undifferentiated disease, multimorbidity, and chronic disease
2. family medicine is a community-based discipline
   - responds/adapts to changing needs and circumstances of the community, with emphasis on injury/disease prevention and health promotion
   - sees patients across their lifespan, with a variety of diseases, in a variety of clinical contexts, collaboratively with a network of multidisciplinary community healthcare providers
3. the family physician is a resource to a defined practice population
   - engages in self-directed, lifelong learning to ensure relevance of practice in maintaining patient health
   - advocates for public policy that promotes health, resource stewardship, and the continuity and coordination of care
4. the patient-physician relationship is central to the role of the family physician
   - commits to the whole person, not just the disease, in the context of the patient's family and wider social environment
   - promotes continuity of patient care, respecting patient privacy and the physician-patient relationship

Experts in Generalism

Generalism is a professional philosophy of care, distinguished by a commitment to holistic, integrated, person-centred care, the broadest scope of practice, and collaboration with the larger health care team in order to respond to patient and community health needs. Family physicians are the quintessential experts in generalism with an emphasis on patient- and family-centred care, community adaptiveness, undifferentiated problems, management of uncertainty, prevention and health promotion, multimorbidity/chronic disease, and longitudinal aspects of health and illness.

Periodic Health Examination

- the Canadian Task Force on Preventive Health Care was established in 1976 to develop and disseminate clinical practice guidelines for primary and preventive care, and provides:
  - recommendations based on systematic analysis of scientific evidence
  - periodic preventive health visits recommended in place of annual physical examinations (sometimes called "yearly physicals")

Purpose of the Periodic Health Examination

- primary prevention: identify risk factors for common diseases; counsel patients on health-promoting practices (e.g. vaccinations)
- secondary prevention: early detection of disease to allow prompt treatment and prevent disease progression (e.g. screening programs)

Classification of Recommendations (GRADE)

Strength of Recommendation

- strong: confidence that desirable effects outweigh undesirable effects (strong recommendation for an intervention) or that the undesirable effects outweigh desirable effects (strong recommendation against an intervention)
  - implies that most individuals will be best served by the recommended course of action
- conditional: desirable effects probably outweigh the undesirable effects (conditional recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (conditional recommendation against an intervention)
  - implies that most people would want the recommended course of action but that many would not
  - different choices will be appropriate for different individuals, patients require support in reaching a management decision consistent with their values and preferences

Quality of Evidence

- high: high level of confidence that true effect lies close to the estimate of the effect
- moderate: true effect likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- low or very low: true effect may be substantially different from the estimate of the effect

Table 1. Periodic Health Exam

	General Population	Special Population
Discussion	Dental hygiene (community fluoridation, brushing, flossing) (A) Noise control and hearing protection (A) Screen for poverty Counsel on smoking cessation and provide nicotine replacement therapy (A), referral to smoking cessation program (B) Dietary advice on leafy green vegetables and fruits (B) Seat belt use (B) Moderate physical activity (B) Avoid sun exposure and wear protective clothing (B) Problem drinking screening and counselling (B) Counselling to protect against STIs (B) Nutritional counselling, dietary advice on fat and cholesterol (B) Dietary advice on calcium and vitamin D requirements (B)	**Pediatrics**: home visits for high-risk families (A), injury prevention (home visits for high-risk families (A), injury prevention (poison control, smoke detectors, non-flammable sleepwear, hot water thermostat settings) (B), inquiry into developmental milestones (B) **Adolescents**: counsel on sexual activity and contraceptive methods (B), counsel to prevent smoking initiation and substance use (B) **Perimenopausal Women (>50)**: assess for risk factors for: osteoporosis and fracture (A), counsel on osteoporosis, counsel on risks/benefits of hormone replacement therapy (B) **Adults >65**: follow up on caregiver concern of cognitive impairment (A), multidisciplinary post-fall assessment (A)
Physical	BP measurement, using techniques described in CHEP guidelines (A) Measure height, weight, and calculate BMI for adults ≥18 (B)	**Pediatrics**: repeated examinations of hips, eyes, and hearing (especially in first year of life) (A), serial height, weight, and head circumference (B), visual acuity testing after age 2 (B) **Adults >65**: hearing impairment (inquiry, whispered voice test, audioscope) (B) **First-Degree Relative with Melanoma**: full body skin exam (B)

Classification of recommendation in brackets: A – high quality of evidence; B – moderate quality of evidence. For up-to-date guidelines, see: www.canadiantaskforce.ca.

References:
Guidelines [Internet]. Ottawa (ON): The Canadian Task Force on Preventive Health Care; c2019 [cited 2021].
Available from: https://canadiantaskforce.ca/guidelines/
Zaltzman A, Dubey V, Iglar K. Update to the Preventive Care Checklist Form©. CFP. 2020 Apr 1;66(4):270-2.

Adult Periodic Health Exam
Male and female evidence-based preventive care checklist forms are available online athttp://www.cfpc.ca, most recently updated in 2018, re-endorsed in 2019.

Choosing Wisely Canada
http://www.choosingwiselycanada.org/
"A campaign to help clinicians and patients engage in conversations about unnecessary tests and treatments, and make smart and effective choices to ensure high quality care."

Folic Acid Supplementation in Pregnancy (Joint Society of Obstetricians and Gynecologists of Canada-Motherisk Clinical Guideline May 2015)

- To prevent neural tube defects in all women capable of becoming pregnant
- Low-risk women (no personal health risks, planned pregnancy): diet of folate-rich foods and a daily oral multivitamin supplement containing 0.4-1.0 mg folic acid for at least 2-3 mo before conception, throughout pregnancy, and 4-6 wk postpartum or as long as breast-feeding continues
- High-risk women (health risks including epilepsy, insulin-dependent diabetes, BMI >35, family history of NTD, high-risk ethnic group): diet of folate-rich foods and daily supplementation with multivitamins with 5 mg folic acid at least 3 mo prior to conception until 12 wk post-conception
- From wk 12 post-conception until postpartum period (4-6 wk or as long as breastfeeding continues): 0.4-1.0 mg of folic acid supplementation is sufficient
- Women with additional lifestyle issues (poor compliance with medications, no consistent birth control, taking possible teratogenic substances): higher folic acid dose of 5 mg and counselling about prevention of birth defects

Table 1. Periodic Health Exam

	General Population	Special Population
Tests	See recommendations below for age and gender specific screening for diabetes, dyslipidemia, HTN, and cancer screening (colon, prostate, cervical, lung, and breast) One-time screening ultrasound for abdominal aortic aneurysm in men aged 65–80 yr (B)	**Pediatrics**: routine hemoglobin for high-risk infants (B), blood lead screening of high-risk infants (B) **TB High-Risk Groups**: Mantoux skin testing (A) **STI High-Risk Groups**: voluntary HIV antibody screening (A), gonorrhea screening (A), chlamydia screening in women (B), syphilis screening (A) **Syphilis High-Risk Groups**: VDRL test (A)
Therapy	Folic acid supplementation for women of child-bearing age (A) Pharmacologic treatment of HTN (refer to CHEP Guidelines) (A) Varicella vaccine for children ages 1-12 and susceptible adolescents/adults (A) Rubella vaccine for all non-pregnant women of child-bearing age unless there is proof of immunity via immunization records or serology (B) Tetanus vaccine: routine booster q10 yr if had 1° series (A) Pertussis vaccine: adults <65 should receive one booster given as Tdap– Adacel® or Boostrix® (A) Herpes zoster vaccine for adults ≥50 (A)	**Pediatrics**: routine immunizations (A) **Influenza High-Risk Groups**: outreach strategies for vaccination (A), annual immunization (B), now recommended for all **HPV High-Risk Groups**: vaccination for males and females from age 9 with no upper age limit, if ongoing risk **TB High-Risk Groups**: INH prophylaxis for household contacts or skin test converters (B), INH prophylaxis for high-risk sub-groups (B) **Immunocompromised/Ages ≥65/COPD/Asthma/CHF/Asplenia/Liver Disease/Renal Failure/DM**: pneumococcal vaccine (Pneumovax® 23) for all ≥65 or high-risk, add Prevnar®13 if ≥65 and high-risk (A)

Classification of recommendation in brackets: A – high quality of evidence; B – moderate quality of evidence. For up-to-date guidelines, see: www.canadiantaskforce.ca.
References:
Guidelines [Internet]. Ottawa (ON): The Canadian Task Force on Preventive Health Care; c2019 [cited 2021].
Available from: https://canadiantaskforce.ca/guidelines/
Zaltzman A, Dubey V, Iglar K. Update to the Preventive Care Checklist Form©. CFP. 2020 Apr 1;66(4):270-2.

Breast Cancer Screening Guidelines

2018 Canadian Task Force on Preventive Care Recommendations
- for women ages 50-74, recommend screening with mammography every 2-3 yr; the decision to undergo screening is conditional on the relative value that a woman places on possible benefits and harms from screening (conditional recommendation; very low certainty evidence)
- for women ages 40-49, recommend not screening with mammography; the decision to undergo screening is conditional on the relative value that a woman places on possible benefits and harms from screening (conditional recommendation; low certainty evidence)
- recommend not performing clinical breast examinations to screen for breast cancer (conditional recommendation; no evidence)
- recommend not advising women to practice breast self-examination to screen for breast cancer (conditional recommendation; low certainty evidence)
- recommend not using MRI, tomosynthesis, or U/S to screen for breast cancer in women not at increased risk (strong recommendation; no evidence)
- for more information on benign breast lesions and breast cancer, see General Surgery and Thoracic Surgery, GS66

Lung Cancer Screening Guidelines

2016 Canadian Task Force on Preventive Health Care Recommendations
- for adults ages 55-74 with ≥30 pack-yr smoking history who currently smoke or quit ≤15 yr ago, recommend annual screening with LDCT up to three consecutive times; screening should ONLY be carried out in health care settings with expertise in early diagnosis and treatment of lung cancer (weak recommendation; low quality evidence)
- for all other adults, regardless of age, smoking history, or other risk factors, recommend not screening for lung cancer with LDCT (strong recommendation; very low quality evidence)
- recommend that chest x-ray not be used to screen for lung cancer, with or without sputum cytology (strong recommendation; low quality evidence)

Colorectal Cancer Screening Guidelines

2016 Canadian Task Force on Preventive Health Care Recommendations

- recommend screening adults ages 60-74 for CRC with FOBT (either gFOBT or FIT) q2 yr OR flexible sigmoidoscopy q10 yr (strong recommendation; moderate quality evidence)
- recommend screening adults ages 50-59 for CRC with FOBT (either gFOBT or FIT) q2 yr OR flexible sigmoidoscopy q10 yr (weak recommendation; moderate quality evidence)
- recommend not screening adults ages ≥75 for CRC (weak recommendation; low quality evidence)
- recommend not using colonoscopy as a screening test for CRC (weak recommendation; low quality evidence)

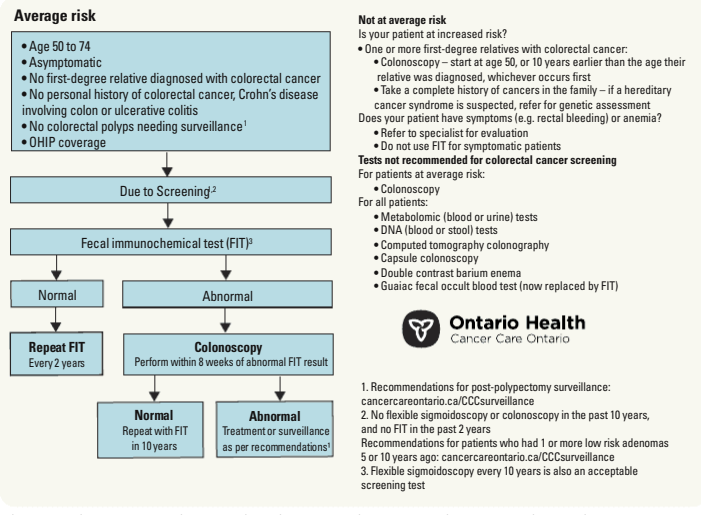

Average risk
• Age 50 to 74
• Asymptomatic
• No first-degree relative diagnosed with colorectal cancer
• No personal history of colorectal cancer, Crohn's disease involving colon or ulcerative colitis
• No colorectal polyps needing surveillance[1]
• OHIP coverage
Due to Screening[2]
Fecal immunochemical test (FIT)[3]
Normal
Abnormal
Repeat FIT
Every 2 years
Colonoscopy
Perform within 8 weeks of abnormal FIT result
Normal
Repeat with FIT in 10 years
Abnormal
Treatment or surveillance as per recommendations[1]
Not at average risk
Is your patient at increased risk?
• One or more first-degree relatives with colorectal cancer:
• Colonoscopy – start at age 50, or 10 years earlier than the age their relative was diagnosed, whichever occurs first
• Take a complete history of cancers in the family – if a hereditary cancer syndrome is suspected, refer for genetic assessment
Does your patient have symptoms (e.g. rectal bleeding) or anemia?
• Refer to specialist for evaluation
• Do not use FIT for symptomatic patients
Tests not recommended for colorectal cancer screening
For patients at average risk:
• Colonoscopy
For all patients:
• Metabolomic (blood or urine) tests
• DNA (blood or stool) tests
• Computed tomography colonography
• Capsule colonoscopy
• Double contrast barium enema
• Guaiac fecal occult blood test (now replaced by FIT)
Ontario Health
Cancer Care Ontario
1. Recommendations for post-polypectomy surveillance: cancercareontario.ca/CCCsurveillance
2. No flexible sigmoidoscopy or colonoscopy in the past 10 years, and no FIT in the past 2 years
Recommendations for patients who had 1 or more low risk adenomas 5 or 10 years ago: cancercareontario.ca/CCCsurveillance
3. Flexible sigmoidoscopy every 10 years is also an acceptable screening test

Figure 1. Guide to average risk screening with the fecal immunochemical test (FIT) in Ontario
Colon Cancer Check 2019 Guide to Average Risk Screening with the Fecal Immunochemical Test (FIT) in Ontario. Reproduced with permission from Cancer Care Ontario. Available from https://www.cancercareontario.ca/sites/ccocancercare/files/assets/H-FIT_PCC_2742_ClinicalToolForProviders.pdf

Cervical Cancer Screening Guidelines

2013 Canadian Task Force for Preventive Care Guidelines Recommendations

- for women ages <20, recommend not routinely screening for cervical cancer (strong recommendation; high quality evidence)
- for women ages 20-24, recommend not routinely screening for cervical cancer (weaek recommendation; moderate quality evidence)
- for women ages 25-29, recommend Papanicolaou (Pap) smear or liquid cytology for cervical cancer q3 yr (weak recommendation; moderate quality evidence)
- for women ages 30-69, recommend Pap smear or liquid-based cytology for cervical cancer q3 yr (strong recommendation; high quality evidence)
- for women ages ≥70 who have not been adequately screened, recommend continued screening until 3 negative test results have been obtained (weak recommendation; low quality evidence)
- for women ages ≥70 who have been adequately screened (i.e. 3 successive negative Pap tests in the last 10 yr), recommend that routine screening may cease
- for more information on cervical cancer (see Gynecology, GY47)
- note: provincial/territorial guidelines vary, e.g. Ontario Cervical Screening Program (2022):
  - women ages ≥25 who are or have ever been sexually active, recommend screening q3 yr (if cytology normal);
  - women ages ≥21 may initiate screening if they are immunocompromised and are or have ever been sexually active

The Canadian Task Force on Preventive Health Care is anticipating the publication of new cervical cancer screening guildelines in 2023. Please refer to the published Systematic Review Protocol for the new guidelines: https://canadiantaskforce.ca/wp-content/uploads/2021/11/Task-Force_Cervical-Cancer_SystematicReviewProtocol.pdf

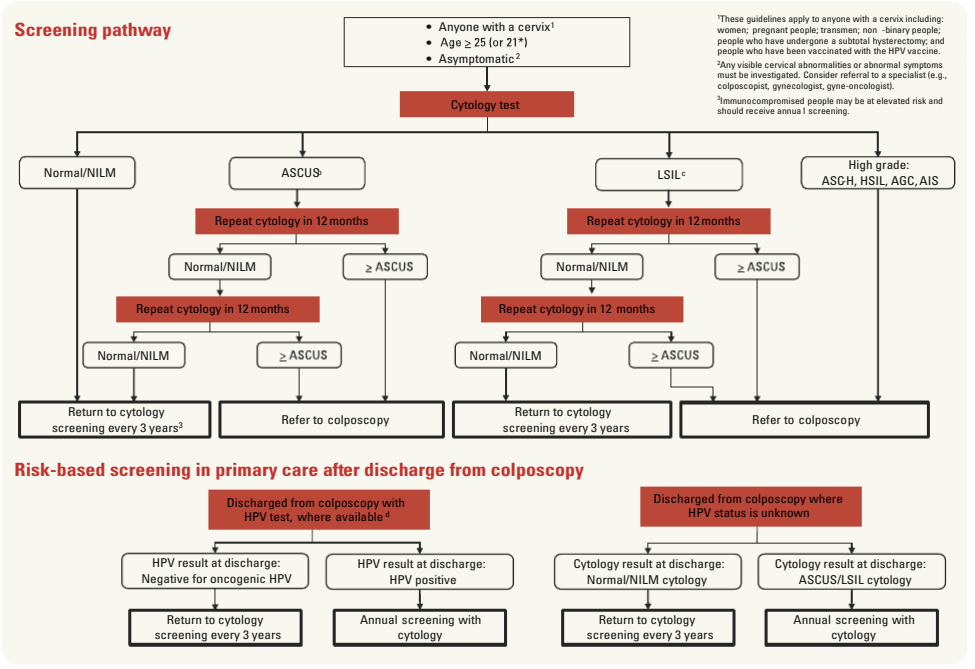

Screening pathway
Anyone with a cervix[1]
Age ≥ 25 (or 21*)
Asymptomatic[2]
Cytology test
[1]These guidelines apply to anyone with a cervix including: women; pregnant people; transmen; non -binary people; people who have undergone a subtotal hysterectomy; and people who have been vaccinated with the HPV vaccine.
[2]Any visible cervical abnormalities or abnormal symptoms must be investigated. Consider referral to a specialist (e.g., colposcopist, gynecologist, gyne-oncologist).
[3]Immunocompromised people may be at elevated risk and should receive annual screening.
Normal/NILM
ASCUS[b]
LSIL[c]
High grade: ASC-H, HSIL, AGC, AIS
Repeat cytology in 12 months
Repeat cytology in 12 months
Normal/NILM
≥ ASCUS
Normal/NILM
≥ ASCUS
Repeat cytology in 12 months
Repeat cytology in 12 months
Normal/NILM
≥ ASCUS
Normal/NILM
≥ ASCUS
Return to cytology screening every 3 years[3]
Refer to colposcopy
Return to cytology screening every 3 years
Refer to colposcopy
Risk-based screening in primary care after discharge from colposcopy
Discharged from colposcopy with HPV test, where available[d]
Discharged from colposcopy where HPV status is unknown
HPV result at discharge: Negative for oncogenic HPV
HPV result at discharge: HPV positive
Cytology result at discharge: Normal/NILM cytology
Cytology result at discharge: ASCUS/LSIL cytology
Return to cytology screening every 3 years
Annual screening with cytology
Return to cytology screening every 3 years
Annual screening with cytology

Figure 2. Ontario screening pathway for cervical cancer

AGUS = atypical glandular cells of unknown significance; ASCUS = abnormal squamous cells of unknown significance; ASC-H = abnormal squamous cells cannot rule out HSIL; HSIL = high grade squamous intraepithelial lesion; LSIL = low grade squamous intraepithelial lesion; AGC = atypical glandular cells; AIS = adenocarcinoma in-situ; TZ = transitional zone

Adapted from: Ontario Cervical Screening Program 2022 Screening Recommendations Summary. Reproduced with permission from Cancer Care Ontario. Retrieved from https://www.cancercareontario.ca/en/system/files_force/derivative/OCSPScreeningGuidelines.pdf

Prostate Cancer Screening Guidelines

2014 Canadian Task Force for Preventive Care Guidelines Recommendations

- for men ages 55-69, recommend not screening for prostate cancer with the PSA test (weak recommendation; moderate quality evidence); clinicians should discuss the risks and benefits of screening and its potential consequences with each man in the context of his preferences
- for men ages ≤55, recommend not screening for prostate cancer with the PSA test (strong recommendation; low quality evidence)
- for men ages ≥70, recommend not screening for prostate cancer with the PSA test (strong recommendation; low quality evidence)

Basis of Recommendation

- the potential small benefit from PSA screening is outweighed by the potential significant harms of the screening and associated follow-up treatment
  - for men ages ≤55 or ≥70, there is no evidence that screening with the PSA test reduces mortality, whereas there is evidence of harms
  - for men ages 55-69, there is inconsistent evidence of a small potential benefit of screening and evidence of harms

The Canadian Task Force on Preventive Health Care is anticipating the publication of new prostate cancer screening guidelines in 2024/2025. Please refer to the published Systematic Review Protocol for the new guidelines: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-022-02099-9

Health Promotion and Counselling

- health promotion is the most effective preventive strategy
- initial steps should include to respectfully explore the values and purposes of the patient's habits or behaviours
- it is helpful to be guided by a patient's present stage of change when having discussions around healthy behaviours
- for more information, see www.motivationalinterviewing.org

Motivational Strategies for Behavioural Change

Table 2. Motivational Strategies for Behavioural Change

Patient's Stage of Change	Physician's Aim	Physician's Plan
Pre-Contemplation	Encourage patient to consider the possibility of change Assess readiness for change Increase patient's awareness of the problem and its risks	Raise issue in a sensitive manner Offer (not impose) a neutral exchange of information to avoid resistance
Contemplation	Understand patient's ambivalence and encourage change Build confidence and gain commitment to change	Offer opportunity to discuss pros and cons of change using reflective listening
Preparation	Explore options and choose course most appropriate for the patient Identify high-risk situations and develop strategies to prevent relapse Continue to strengthen confidence and commitment	Offer realistic options for change and opportunity to discuss inevitable difficulties
Action	Help patients design rewards for success Develop strategies to prevent relapse Support and reinforce convictions towards long-term change	Offer positive reinforcement and explore ways of coping with obstacles Encourage self-rewards to positively reinforce change
Maintenance	Help patient maintain motivation Review identified high-risk situations and strategies for preventing relapse Increase self-belief in ongoing change	Discuss progress and signs of impending relapse
Relapse	Help patient view relapse as a learning experience Provide support appropriate to re-entry into the change cycle at the patient's present level of readiness, post-relapse	Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future Reassess patient's readiness to change

Adapted from: Hunt P. Motivating Change. Nurs Stand 2001;16:45-52, 54-55

Canadian Cancer Society Recommendations for Vitamin D Use

Based on CCS research on Vitamin D and the prevention of colorectal and breast cancers

In consultation with their healthcare provider, the Society recommends that:

- Adults living in Canada should consider taking Vitamin D supplementation of 1000 IU/d during the fall and winter
- Adults at higher risk of having lower Vitamin D levels should consider taking Vitamin D supplementation of 1000 IU/d all year round. This includes people: who are older, with dark skin, who do not go outside often, and who wear clothing that covers most of their skin
- Babies who are exclusively breast-fed: 400 IU/d

Nutrition

General Population

- Canada's Food Guide is appropriate for individuals ages ≥2 yr
- counsel on variety, portion size, and plate layout
- guideline 1: nutritious foods are the foundation for healthy eating. Vegetables, fruits, whole grains, and proteins should be consumed regularly. Among protein foods, consume plant-based more often (e.g. legumes, nuts, seeds, tofu, fortified soy beverage). Foods with mostly unsaturated fat should replace those that contain mostly saturated fat. Water should be beverage of choice
  - nutritious foods to consume regularly can be fresh, frozen, canned, or dried
  - consider cultural preferences and food traditions. Traditional food improves diet quality among Indigenous peoples
- guideline 2: processed or prepared foods and beverages that contribute to excess sodium, free sugars, or saturated fat undermine healthy eating, and should not be consumed regularly
- guideline 3: food skills are needed to navigate the complex food environment and support healthy eating. Cooking and food preparation using nutritious foods should be promoted. Food labels should be promoted as a tool to help make informed choices

Energy Content of Food

- Carbohydrates: 4 kcal/g
- Protein: 4 kcal/g
- Fat: 9 kcal/g
- Ethanol: 7 kcal/g

Calculating Total Daily Energy Expenditure

Roughly 35 kcal/kg/d

Varies by age, weight, height, sex, and activity level

Average 2000-2100 kcal/d for women, 2700-2900 kcal/d for men

Handy Serving Size Comparisons

85 g meat, fish, poultry → palm of hand

250 ml dairy (milk/yogurt) → size of fist

1 serving of bread/grains → one slice, palm of hand

125 g rice/pasta → one hand cupped

250 g of fruit/vegetables → two cupped hands

28 g cheese → full length of thumb

5 g oil/butter → tip of thumb

28-57 g nuts/chips/snacks→ palm covered

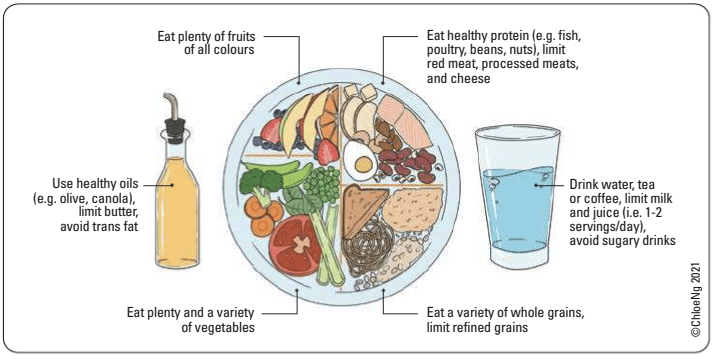

Eat plenty of fruits of all colours
Eat healthy protein (e.g. fish, poultry, beans, nuts), limit red meat, processed meats, and cheese
Use healthy oils (e.g. olive, canola), limit butter, avoid trans fat
Drink water, tea or coffee, limit milk and juice (i.e. 1-2 servings/day), avoid sugary drinks
Eat plenty and a variety of vegetables
Eat a variety of whole grains, limit refined grains
©ChloeNg 2021

Figure 3. Canada's Food Guide 2019 - plate layout
Source: © All Rights Reserved. Canada's Food Guide. Health Canada, 2019. Adapted and reproduced with permission from the Minister of Health, 2019.

Osteoporosis Canada Recommendations for Calcium and Vitamin D Daily Requirements
Vitamin D: 400-1000 IU for individuals 19-50 yr, 800-2000 IU for individuals ≥50 yr or younger adults at high-risk (osteoporosis, multiple fractures, inadequate vitamin D absorption)
Calcium: 1000 mg daily from all sources for individuals 19-50 yr and pregnant/lactating women; 1200 mg daily for individuals >50 yr (recommended to obtain calcium from diet whenever possible vs. supplementation)

Cardiovascular Disease Prevention

Table 3. Dietary Guidelines for Reducing Risk of Cardiovascular Disease

Carbohydrates	Complex carbs (legumes, whole grains) should be favoured over simple carbs (white flour/rice, table sugar) Eliminate sugar-sweetened beverages in favour of water
Fruits and Vegetables	Consume a higher proportion of whole, fresh fruits and vegetables Consume leafy green vegetables and berries at least 3 times/wk Consume starchy vegetables (white potatoes, corn, green peas) in moderation
Fats	Consume mono- and polyunsaturated fats in moderation (non-tropical vegetable fats, liquid fats) Minimize trans fat intake (processed/snack foods) Limit saturated fats (processed foods, red meat, cheese, whole milk, butter) Olive and canola oil are recommended over butter/margarine/coconut oil Skim or 1% milk is recommended over whole milk
Protein	Consume fish with higher levels of omega-3 fatty acids (salmon, tuna, mackerel) Moderate consumption of lean poultry, seafood, and nuts Limit red meat Minimize consumption of processed meats (deli/cold cuts, sausage, bacon)
Salt	≤2000 mg/d
Alcohol	Recommend limiting drinks to ≤2/wk. There is a continuum of risk associated with alcohol consumption where the risk of harm from alcohol is: Low - ≤2 drinks/wk Moderate - 3-6 drinks/wk High ≥7 drinks/wk
Dietary Approaches	**Mediterranean diet:** High intake of leafy green vegetables, fruits, whole grains, nuts, legumes, extra virgin olive oil Moderate intake of fish, lean meats, low fat dairy, poultry Low intake of red meats and sweets **DASH diet:** High in vegetables/fruits, no or low-fat dairy, whole grains, poultry, fish, beans, seeds, and nuts Low in sodium, sweets, added sugars, sugar-sweetened beverages, fats, and red meats Lower in saturated fat, trans fat, and cholesterol High in potassium, magnesium, calcium, protein, and fibre **Vegetarian diet:** Substitute meat/seafood/poultry with soy products, legumes, nuts, and whole grains

Dietary approaches to stop hypertension (DASH), available from: http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/dash_brief.pdf
Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.
Pallazola VA, et al. A Clinician's Guide to Healthy Eating for Cardiovascular Disease Prevention. Mayo Clin Proc Innov Qual Outcomes 2019;3:251-267.
Anderson TJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 2016;32:1263-1282.
Paradis C, et al. Canada's Guidance on Alcohol and Health: Final Report. Canadian Centre on Substance Use and Addiction 2023.

Obesity

Definition

- prevalent, complex, progressive, and relapsing chronic disease that is characterized by abnormal/excessive body fat (adiposity)
- impairs health, increases risk of long-term medical complications, and reduces lifespan

Epidemiology

- in Canada, the prevalence of obesity has tripled and severe obesity has more than quadrupled since 1985
- obesity remains higher in populations which face multiple socioeconomic barriers such as geographic isolation, poverty, and lack of access to nutritious (and more expensive) food
- for example, First Nations living on reserves have higher rates of obesity (30-51%) than non-Indigenous populations (12-31%)
- close to 1/3 of Canadians ages 5-17 yr were identified as having a BMI classified as overweight or obese
- screen time ≥2 h/d (total screen time, television time, and computer time) is likely associated with an increased risk of children having a BMI classified as overweight or obese

2015 Canadian Task Force on Preventive Health Care Recommendations

- for apparently healthy adults ≥18 yr, it is recommended to measure height, weight, and calculate BMI at appropriate primary care visits
  - BMI = weight (kg)/height ^{2}(m ^{2}) = weight (lbs)/height ^{2}(in ^{2}) x 703
  - note: this recommendation does not apply to people with eating disorders or who are pregnant
- for those with increased BMI (25.0-34.9 kg/m ^{2}), WC should be measured regularly to identify patients with increased visceral adiposity and related health risks
- for apparently healthy children and youth ages 0-17 yr, it is recommended to monitor growth at all appropriate primary care visits using the 2014 WHO Growth Charts for Canada (strong recommendation; very low quality evidence). This recommendation does not apply to children and youth with eating disorders, or who are underweight, overweight, or obese

Table 4. Classification of Weight by Body Mass Index and Associated Disease Risks in Adults

	BMI (kg/m^2)	Risk of Developing Health Problems
Underweight	<18.5	Increased
Normal	18.5-24.9	Least
Overweight	25.0-29.9	Increased
Obesity Class I	30.0-34.9	High
Obesity Class II	35.0-39.9	Very high
Obesity Class III (Extreme Obesity)	≥40.0	Extremely high

Body Mass Index (BMI) Nomogram, Government of Canada: Health Canada, available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/healthy-weights/canadian-guidelines-body-weight-classification-adults/body-mass-index-nomogram.html

Management

Canadian Adult Obesity Clinical Practice Guidelines (Obesity Canada, 2020)

- recognize that people with obesity experience weight bias and stigma, which contributes to increased complications and mortality independent of weight or BMI
- **Step 1** - Ask: recognize obesity as a chronic disease and obtain patient permission to discuss and help treat this disease in an unbiased manner
- **Step 2** - Assess: assess the patient using appropriate measures (i.e. height, weight, WC, and BMI calculation) and identify root causes (e.g. biological factors, individual life experiences, psychological factors), complications, and barriers to treatment
- **Step 3** - Advise: discuss treatment options and work with the patient to create individualized care plans that address root causes of obesity and support behaviour change
  - nutrition:
    - all individuals can benefit from adopting a healthy, well-balanced diet
    - weight loss requires long-term reduction in caloric intake, encouraged by a personalized eating pattern that meets the patient's values, preferences, and nutritional needs
    - medical nutrition therapy should not be used in isolation (may promote compensatory mechanisms that promote positive caloric intake by increasing hunger), but instead should be used in combination with other interventions (e.g. psychological, pharmacological, surgical)
  - physical activity:
    - consider aerobic physical activity (30-60 min of moderate to vigorous intensity most d/wk) for adults who wish to achieve small amounts of body weight and fat loss, reduce abdominal visceral fat, maintain weight loss, and/or increase cardiorespiratory fitness
    - resistance training may promote weight maintenance, increased muscle mass, fat-free mass, and mobility in adults who are overweight/obesity
    - regular physical activity can improve cardiometabolic risk factors and improve health-related quality of life
  - psychological and behavioural interventions:
    - multicomponent psychological intervention (behaviour modification, cognitive therapy, and values-based strategies to alter diet/activity) should be incorporated into care plans for weight loss

Treatment for Overweight and Obesity in Adult Populations: A Systematic Review and Meta-analysis
CMAJ Open 2014;2:E306-317
Purpose: To evaluate the effectiveness of behavioural and pharmacological treatments for overweight and obese adults.
Methods: Review of RCTs of primary-care-relevant behavioural (diet, exercise, lifestyle) and pharmacological (orlistat, metformin) treatments with or without behavioural interventions in overweight or obese adults with 12 mo follow-up from baseline for weight outcomes or harms. Secondary health outcomes (TC, LDL, FBG, incidence of T2DM, sBP and dBP) were also studied.
Results: 68 RCTs were included and showed that intervention participants had greater weight loss (-3.02 kg, 95% CI -3.52 to -2.52), waist circumference reduction (-2.78 cm, 95% CI -3.34 to -2.22) and BMI reduction (-1.11 kg/m2, 95% CI -1.39 to -0.84). Relative risk for weight loss of ≥5% body weight was 1.77 (95% CI 1.58 to 1.99; NNT 5, 95% CI 4-7). Relative risk for loss of ≥10% body weight was 1.91 (95% CI 1.69 to 2.16; NNT 9, 95% CI 7-12). Incidence of T2DM was lower among pre-diabetic intervention participants (RR 0.62, 95% CI 0.50 to 0.77; NNT 17, 95% CI 13-29).
Conclusion: Behavioural and pharmacological treatments for overweight and obese adults may lead to clinically important reductions in weight and incidence of T2DM in pre-diabetic populations.

Adverse Medical Consequences of Obesity

- T2DM
- Dyslipidemia
- CAD
- Osteoarthritis
- Stroke
- OSA
- HTN
- Certain cancers
- Gallbladder disease
- CHF
- Low back pain
- Non-alcoholic statohepatitis
- Increased total mortality
- Pregnancy complications

Associations with Low BMI

- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications

Pharmacotherapy for Obesity
There are currently 3 prescription medications available in Canada that are approved for use in adult patients with BMI ≥30 kg/m2 or BMI ≥27 kg/m2 and ≥1 weight-related condition (e.g. HTN, T2DM, dyslipidemia)
Note: these medications should be used alongside a reduced-calorie diet and increased physical activity
Contrave® (naltrexone and bupropion): controls hunger and cravings
Saxenda® (liraglutide): decreases appetite and, therefore, food intake
Xenical® (orlistat): reduces dietary fat absorption by 30% through inhibition of pancreatic and gastric lipases

- pharmacotherapy:
  - liraglutide, naltrexone-bupropion combination, or orlistat (see sidebar *Pharmacotherapy for Obesity, FM9*)
  - can be used for patients with BMI ≥30 kg/m2 or ≥27 kg/m2 with adiposity-related complications, in combination with medical nutrition therapy, physical activity, and psychological interventions
  - can be used to maintain weight loss achieved by behaviour changes and to prevent weight regain
- bariatric surgery:
  - consider for patients with BMI ≥40 kg/m2 or BMI ≥35 kg/m2 with ≥1 adiposity-related disease (e.g. T2DM)
  - consider for weight loss and/or to control adiposity-related diseases where optimal medical and behavioural management has been insufficient to produce significant weight loss
  - choice of bariatric procedure should be decided according to the patient's needs, in collaboration with an experienced interprofessional team (suggest against adjustable gastric banding and single anastomosis gastric bypass, due to unacceptable complications and long-term failure)

- **Step 4** - Agree: agree on goals of therapy with the patient, focusing on the patient's values to ensure realistic expectations, sustainable behaviour change, and improved health outcomes
- **Step 5** - Assist: follow up and reassess the patient regularly to assist with drivers/barriers and advocate for improved obesity care

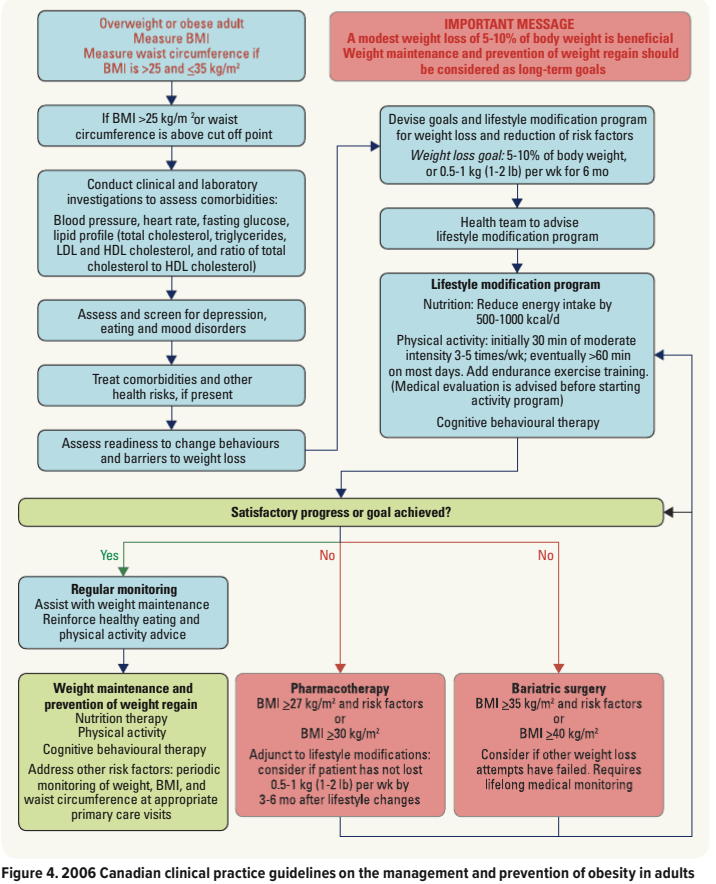

Overweight or obese adult
Measure BMI
Measure waist circumference if BMI is >25 and ≤35 kg/m²
IMPORTANT MESSAGE
A modest weight loss of 5-10% of body weight is beneficial
Weight maintenance and prevention of weight regain should be considered as long-term goals
If BMI >25 kg/m ²or waist circumference is above cut off point
Conduct clinical and laboratory investigations to assess comorbidities:
Blood pressure, heart rate, fasting glucose, lipid profile (total cholesterol, triglycerides, LDL and HDL cholesterol, and ratio of total cholesterol to HDL cholesterol)
Assess and screen for depression, eating and mood disorders
Treat comorbidities and other health risks, if present
Assess readiness to change behaviours and barriers to weight loss
Devise goals and lifestyle modification program for weight loss and reduction of risk factors
Weight loss goal: 5-10% of body weight, or 0.5-1 kg (1-2 lb) per wk for 6 mo
Health team to advise lifestyle modification program
Lifestyle modification program
Nutrition: Reduce energy intake by 500-1000 kcal/d
Physical activity: initially 30 min of moderate intensity 3-5 times/wk; eventually >60 min on most days. Add endurance exercise training. (Medical evaluation is advised before starting activity program)
Cognitive behavioural therapy
Satisfactory progress or goal achieved?
Yes
No
No
Regular monitoring
Assist with weight maintenance
Reinforce healthy eating and physical activity advice
Weight maintenance and prevention of weight regain
Nutrition therapy
Physical activity
Cognitive behavioural therapy
Address other risk factors: periodic monitoring of weight, BMI, and waist circumference at appropriate primary care visits
Pharmacotherapy
BMI ≥27 kg/m² and risk factors
or
BMI ≥30 kg/m²
Adjunct to lifestyle modifications: consider if patient has not lost 0.5-1 kg (1-2 lb) per wk by 3-6 mo after lifestyle changes
Bariatric surgery
BMI ≥35 kg/m² and risk factors
or
BMI ≥40 kg/m²
Consider if other weight loss attempts have failed. Requires lifelong medical monitoring

Figure 4. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children

Adapted from: Lau DCW, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. CMAJ 2007;176:S1-S13

Effects of Popular Diets without Specific Calorie Targets on Weight Loss Outcomes: Systematic Review of Findings from Clinical Trials
Nutrients 2017;9:E822
Purpose: To assess the short-term (≤6 mo) and long-term (≥6 mo) weight loss outcomes for current popular diets in overweight and obese adults.
Methods: A systematic review was conducted. All diets in the 2016 U.S. News & World Report Rankings for "Best Weight-Loss Diets" were examined. From the potential 38 diets, eligible studies included trials with a sample size ≥15 per group, interventional clinical trials, intervention periods ≥12 wk, BMI ≥25 mg/m², participants aged ≥18 yr and objective measures of pre- and post-intervention.
Results: Sixteen articles were included in the review. Diets included the Atkins, DASH, Glycemic-Index, Mediterranean, Ornish, Paleolithic, and Zone diets. The Atkins diet showed the most clinically significant reduction in weight loss in both the short-term and long-term.
Conclusion: Other diets had limited evidence supporting their effectiveness in producing clinically significant short-term and long-term weight loss. Future studies are needed to compare and evaluate the efficacy of these other diets.

Effect of Intermittent Energy and Carbohydrate Restriction vs. Daily Energy Restriction on Weight Loss and Metabolic Disease Risk Markers in Overweight Women
Br J Nutr 2013;110:1534-1547
Purpose: To determine if intermittent energy and carbohydrate restriction (IECR) may result in greater improvements in insulin sensitivity and weight control than daily energy restriction (DER).
Methods: Two IECR regimens were tested, including one which allowed ad libitum protein and fat (IECR + PF). Overweight women (n=115) ages 20-69 with a family history of breast cancer were randomized to an overall 25% energy restriction, or a 25% DER, or an IECR + PF for a 3 mo weight-loss period and 1 mo of weight maintenance (IECR or IECR + PF for 1 d/wk).
Results: Insulin resistance reduced with the IECR diets and the IECR + PF diet. Reductions with the IECR diets were significantly greater compared with the DER diet. Both IECR groups had greater reductions in body fat compared with the DER group. During the weight maintenance phase, 1 day of IECR or IECR + PF per week maintained the reductions in insulin resistance and weight.
Conclusion: In the short term, IECR is superior to DER with respect to improved insulin sensitivity and body fat reduction.

Dyslipidemia

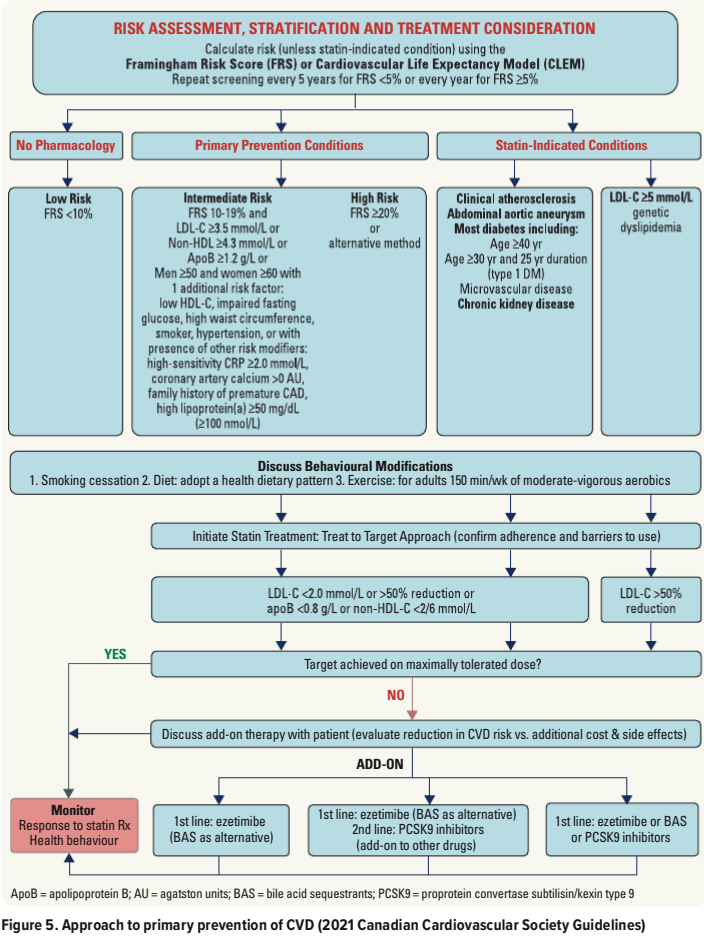

RISK ASSESSMENT, STRATIFICATION AND TREATMENT CONSIDERATION
Calculate risk (unless statin-indicated condition) using the
Framingham Risk Score (FRS) or Cardiovascular Life Expectancy Model (CLEM)
Repeat screening every 5 years for FRS <5% or every year for FRS ≥5%
No Pharmacology
Primary Prevention Conditions
Statin-Indicated Conditions
Low Risk
FRS <10%
Intermediate Risk
FRS 10-19% and
LDL-C ≥3.5 mmol/L or
Non-HDL ≥4.3 mmol/L or
ApoB ≥1.2 g/L or
Men ≥50 and women ≥60 with
1 additional risk factor:
low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension, or with presence of other risk modifiers: high-sensitivity CRP ≥2.0 mmol/L, coronary artery calcium >0 AU, family history of premature CAD, high lipoprotein(a) ≥50 mg/dL (≥100 nmol/L)
High Risk
FRS ≥20%
or
alternative method
Clinical atherosclerosis
Abdominal aortic aneurysm
Most diabetes including:
Age ≥40 yr
Age ≥30 yr and 25 yr duration (type 1 DM)
Microvascular disease
Chronic kidney disease
LDL-C ≥5 mmol/L
genetic dyslipidemia
Discuss Behavioural Modifications
1. Smoking cessation 2. Diet: adopt a health dietary pattern 3. Exercise: for adults 150 min/wk of moderate-vigorous aerobics
Initiate Statin Treatment: Treat to Target Approach (confirm adherence and barriers to use)
LDL-C <2.0 mmol/L or >50% reduction or apoB <0.8 g/L or non-HDL-C <2/6 mmol/L
LDL-C >50% reduction
YES
Target achieved on maximally tolerated dose?
NO
Discuss add-on therapy with patient (evaluate reduction in CVD risk vs. additional cost & side effects)
ADD-ON
Monitor
Response to statin Rx
Health behaviour
1st line: ezetimibe (BAS as alternative)
1st line: ezetimibe (BAS as alternative)
2nd line: PCSK9 inhibitors
(add-on to other drugs)
1st line: ezetimibe or BAS or PCSK9 inhibitors
ApoB = apolipoprotein B; AU = agatston units; BAS = bile acid sequestrants; PCSK9 = proprotein convertase subtilisin/kexin type 9

Figure 5. Approach to primary prevention of CVD (2021 Canadian Cardiovascular Society Guidelines)
Pearson GJ, Thanassoulis G, Anderson T, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2021 Aug;37(8):1129-1150.

• see Endocrinology, E3

Definition

•abnormal elevation of plasma cholesterol or TG levels

Assessment

•screen with full lipid profile every 1-3 yr in males and females ≥40 yr or who are menopausal, or at any age for adults with additional dyslipidemia risk factors (see Clinical Pearl), and in the late postpartum period for women who have had a pregnancy-related complication (e.g. hypertensive disorders of pregnancy, gestational diabetes, preterm birth, stillbirth, low birthweight infant, placental abruption)
•history and physical examination
•measure standard lipid panel (TC, LDL-C, HDL-C, TG, calculated HDL-C), glucose, and eGFR (optional: apolipoprotein B (ApoB), urine ACR)
•screen for secondary causes: hypothyroidism, CKD, DM, nephrotic syndrome, liver disease

Signs of Hyperlipidemia
Atheromata: plaques in the intimal layer of arterial walls
Xanthelasmata: a sharply demarcated yellowish deposit of cholesterol underneath the skin, usually on or around the eyelid
Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
Eruptive xanthoma: hypertriglyceridemia-induced reddish yellow, pruritic, and painful papular or nodular rash
Lipemia retinalis: characterized by creamy, white-coloured retinal blood vessels, occurs only with extreme hypertriglyceridemia
Corneal arcus (arcus senilis): lipid deposit in cornea

To calculate FRS go to https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/

Risk Factors for Screening for Dyslipidemia
- Men and women ages ≥40 (or postmenopausal)
- Increased incidence in Indigenous individuals or individuals of South Asian ancestry
- Current cigarette smoking
- T2DM
- Arterial HTN
- Family history of premature CVD (men <55 yr, women <65 yr in 1st-degree relative)
- Family history of dyslipidemia
- Erectile dysfunction
- CKD
- Inflammatory disease (lupus, RA, psoriatic arthritis, IBD)
- HIV infection
- COPD
- Clinical evidence of atherosclerosis or abdominal aortic aneurysms
- Stigmata of dyslipidemia (arcus cornea, xanthelasma, or xanthoma)
- Obesity (BMI ≥30 kg/m ^{2})
- Hypertensive diseases of pregnancy

Non-Fasting Lipids vs. Fasting Lipids
Non-fasting (TC and non-HDL cholesterol) can be used for Framingham Risk Assessment and hold same prognostic value as fasting lipids
In fasted vs. non-fasted samples, HDL-C and TC vary by <2%, LDL-C varies by <10% and TG varies by <20%
Recently, non-fasting LDL-C has the same prognostic value as fasting LDL-C
Ontario Association of Medical Laboratories Guidelines for Lipid Testing in Adults 2013. Accessed from: https://oaml.com/wp-content/uploads/2016/05/OAMLGuidelineforAdultLipidTestingFinal2013.pdf

LDL cannot be calculated when TG ≥4.5 mmol/L

- risk category
  - estimate using the FRS for assessing 10 yr risk of developing CAD
    - FRS is calculated based on gender, age, HDL-C, TC, sBP, smoking, DM
    - family history of premature CVD (<55 in 1st degree male relative or <65 in 1st degree female relative) doubles FRS
    - to be completed for men and women ages 40-75 every 3-5 yr
    - CV age is calculated as patient's age minus the difference between his or her estimated remaining life expectancy (adjusted for coronary and stroke risk) and the average remaining life expectancy of Canadians of the same age and sex
- used to increase adherence to therapy and reaffirm positive effect of following therapy
  - treatment decisions focus on LDL-C level and/or FRS risk; the alternate primary targets are apolipoprotein B and non-HDL-C
  - if moderate risk and LDL-C <3.5, treatment decision thresholds shifted to apolipoprotein B >1.2 g/L or non-HDL-C >4.3 mmol/L
  - other targets include: TC:HDL-C ratio, apolipoprotein B:apolipoprotein A1 ratio, high-sensitivity CRP (used more for risk stratification of CAD), non-HDL-C, and serum TG levels

Management

- intensity and type of treatment is guided by "risk category" assigned (see *Figure 5, FM11*)
- use decision-making aids such as http://chd.bestsciencemedicine.com/calc2.html

1. Health behaviour interventions (can decrease LDL-C by up to 10%)
   - smoking cessation: likely the most important for preventing CAD
   - dietary modification: reduce saturated fat, red meat, refined sugar, alcohol; consume nuts, fruits/vegetables, poultry, fish
   - physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per wk, in bouts of ≥10 min to reduce CVD risk (see *Table 5, FM13*)
   - employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high-risk patients should start treatment immediately with concurrent health behaviour interventions

2. Pharmacologic therapy
   - for a comparison of dyslipidemia medications, see Endocrinology, E5
   - 1st line monotherapy: statins (β-Hydroxy β-methylglutaryl-CoA, HMG-CoA, reductase inhibitors)
     - risks: myopathy (myalgia, rhabdomyolysis)
     - if severe side effects: ezetimibe (cholesterol absorption inhibitor) can be used for 19% reduction in LDL-C
     - post-acute coronary syndrome: cholesterol absorption inhibitors (e.g. ezetimibe) in addition to simvastatin reduced mortality, attained lipid targets <1.8, and improved outcomes in high-risk individuals

- other agents: bile acid sequestrants, niacin, fibrates, PCSK9 inhibitors
- monitoring
  - ALT, and CK if symptomatic, Cr at baseline then 6 wk later for signs of transaminitis or myositis; tolerate rise in CK up to 10 times upper limit of normal vs. 2-3 times if symptomatic, or serum Cr rise of ≤25%
  - no routine repeated measures of ALT and CK necessary in asymptomatic patients using statin therapy
  - if adequate response is achieved, evaluate fasting lipids every 6-12 mo
  - a target LDL-C <2.0 mmol/L or >50% reduction of LDL-C is the recommended target for therapy to decrease the risk of CVD events and mortality

Isolated Hypertriglyceridemia

- does not increase cardiovascular risk
- normal HDL-C and TC, elevated TG
- mild ≥2.2 mmol/L (≥200 mg/dL); marked ≥5.6 mmol/L (≥500 mg/dL)
- principal therapy is lifestyle modification
  - weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in those with DM, increased omega-3 fatty acid intake
  - severe hypertriglyceridemia (typically >10 mmol/L) is associated with an increased risk of acute pancreatitis
- drug therapy (lowers risk for pancreatitis, not CAD)
  - fibrates

Safety of Statins: An Update
Therapeutic Advances in Drug Safety 2012;3:133-144
Trials have shown that statin therapy slightly increases the incidence of T2DM and hemorrhagic stroke; however, the absolute risk is small. Relative to the reduction in coronary events, their clinical significance is not great enough to recommend against statin use.

Use with caution when prescribing combined statin and fibrate therapy as there has been concern regarding the safety of certain combinations (potential increased risk of myalgias, CK elevations, myopathy, and/or rhabdomyolysis)

Clinical Definition of Metabolic Syndrome
Central obesity
Men – WC ≥94 cm
Women – WC ≥80 cm

Plus any TWO of the following four factors

Risk Factor	Defining Level
TG level	≥1.7 mmol/L (150 mg/dL)
HDL-C level:	
Men	<1.0 mmol/L (40 mg/dL)
Women	<1.3 mmol/L (50 mg/dL)
BP	≥130/85 mmHg or taking BP medications
Fasting glucose level	≥5.6 mmol/L (100 mg/dL)

Statin-Related Adverse Events: A Meta-Analysis
Clin Ther 2006;28:26-35
Purpose: To synthesize adverse event data with statin use based on RCT data.
Methods: Meta-analysis of RCTs focused on adverse effects of statins. Eligible patients were those taking statin monotherapy for primary or secondary prevention of CVD, compared to placebo. Adverse events including elevated liver enzymes or myopathy (myalgias, elevated CK, rhabdomyolysis) were the main outcomes.
Results: Statin therapy increased the risk of any adverse event by 39% (OR 1.4; 95% CI 1.09-1.80; P=0.008) compared with placebo. Treating 1000 patients with a statin would cause 5 adverse events. Serious events (CK >10 times the upper limit of normal or rhabdomyolysis) are infrequent (NNH 3400) and rhabdomyolysis, although serious, is rare (NNH 7428).
Conclusion: Statin therapy was associated with greater odds of adverse events compared with placebo but with substantial clinical benefit. Similar rates of serious adverse events were observed between statin and placebo.

Exercise

Table 5. Canadian 24 Hour Movement Guidelines (2020 CSEP Guidelines)

Age Category	Physical Activity Guidelines	Example Activities	Sleep/Sit Guidelines
Infant (<1)	Active several times daily in a variety of ways Accumulate >30 min/d of tummy time while awake	Interactive floor-based play including tummy time, reaching for toys, crawling	**Sleep**: 14-17 h/d (0-3 mo), 12-16 h/d (4-11 mo) of good quality sleep including naps, with consistent bed and wake up times **Sit**: not restrained (i.e. in a stroller) for >1 h, screen time not recommended, engage in reading/storytelling while sedentary
Toddler (1-2)	Accumulate >180 min of physical activity at any intensity spread throughout the day including energetic play	Moving around the home Climbing stairs Exploring environment Brisk walking, running, dancing	**Sleep**: 11-14 h/d of good quality sleep including naps, with consistent bed and wake up times Sit: not restrained (i.e. in a stroller) for >1 h, sedentary screen time not recommended if <2 yr (<1 h screen time for those ages 2 yr), engage in reading/storytelling while sedentary
Preschool (2-4)	Accumulate >180 min in a variety of activities at any intensity, including ≥60 min of energetic play throughout the day	Moving around the home Climbing stairs Exploring environment Brisk walking, running, dancing	**Sleep**: 10-13 h/d of good quality sleep which may include a nap Sit: not restrained (i.e. in a stroller) for >1 h, sedentary screen time <1 h (less is better), engage in reading/storytelling while sedentary
Children (5-11) and Youth (12-17)	Accumulate >60 min/d of moderate to vigorous aerobic physical activity Muscle/bone strengthening exercises 3 d/wk A variety of structured/unstructured light physical activities for several h/d	Moderate: bike riding, playground playing Vigorous: running, swimming	**Sleep**: 9-11 h/d (5-13 yr), 8-10 h/d (14-17 yr) uninterrupted, with consistent bed and wake up times Sit: no more than 2 h/d of recreational screen time, limit sitting for extended periods
Adults (18-64)	Accumulate 150 min/wk of moderate to vigorous intensity aerobic physical activity, in bouts of ≥10 min Muscle/bone strengthening activities using major muscle groups, ≥2 d/wk	Moderate: brisk walking, bike riding Vigorous: jogging, cross country skiing	**Sleep**: 7-9 h/d of good quality sleep, with consistent bed and wake up times **Sit**: limit sedentary time to 8 h or less, no more than 3 h/d of recreational screen time, break up long periods of sitting as often as possible
Older Adults (≥65)	Same as Adults above Physical activities that challenge balance	Same as Adults above Those with poor mobility should perform physical activities to enhance balance and prevent falls	Same as Adults above

Epidemiology

- 25% of the population exercises regularly, 50% occasionally, 25% is sedentary

Management

- assess current level of fitness, motivation, and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, DM (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, T2DM, osteoporosis, and overweight/obesity
  - leads to improved fitness, strength, mobility, functional independence, and mental health (morale and self-esteem)

Smoking Cessation

Epidemiology

- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2012 Canadian Tobacco Use Monitoring Survey on population ages ≥15
  - 16% are current smokers (lowest since 1985)
  - highest prevalence in those ages 20-24 (20%)
  - 11% of youth ages 15-19 smoke (decreased from 25% in 2000): more males (18%) smoke than females (14%); number of cigarettes consumed per day is also decreasing (15.0 per day in 2012 vs. 16.2 per day in 2001)

Doses, Durations, and Modes of Delivery of Nicotine Replacement Therapy for Smoking Cessation

Cochrane DB Syst Rev 2019;4:CD013308

Purpose: NRT helps with smoking cessation but it is unclear what NRT routines and dosages are most helpful. The aim was to establish efficacy of different forms, deliveries, dosages, and duration of treatment.

Methods: Meta-analysis including RCTs.

Results: High-certainty evidence that combination NRT (fast-acting form + patch) results in higher long-term quit rates than single-form NRT. Moderate-certainty evidence that dosages ≥21/22 mg are equally effective. Five studies comparing 4 mg gum to 2 mg gum found a benefit of the higher dose. Nine studies tested the effect of using NRT prior to quit day (preloading) in comparison to using it from quit day onward; there was moderate-certainty evidence of a favourable effect of preloading on abstinence.

Conclusions: There is high-certainty evidence that using combination NRT vs. single-form NRT can increase the chances of successfully stopping smoking. Higher dosed patches and gum result in higher long term quit rates with moderate-quality evidence.

Management

- general approach
  - identify tobacco users; elicit smoking habits, previous quit attempts, and results
  - be curious about how the patient relates to smoking. Ask: what purpose does smoking serve in their life at the moment?
  - 2012 Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment (CAN-ADAPTT) Guidelines
    - tobacco use status should be updated for all patients regularly
    - health care providers should clearly advise patients to quit
    - health care providers should assess patient willingness to quit and offer assistance to those who express interest
    - health care providers should conduct regular follow-up to assess response and monitor the patient's mental health status/other addictions while quitting smoking
- willing to quit
  - provision of social support, community resources (self-help, group, helpline, web-based strategies)
- medication dosage should be monitored and adjusted as necessary
  - every smoker should be offered treatment
- educate patient to watch for withdrawal symptoms: low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
- combining counselling/behavioural therapies and smoking cessation medication is more effective than either alone
  - ≥4 counselling sessions, >10 min each, with 6-12 mo follow-up yields better results
  - 14% abstinent with counselling vs. 10% without counselling
  - approach depends on patient's stage of change (see *Motivational Strategies for Behavioural Change, FM7*)
- pharmacologic therapy

1. NRT
   - 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
   - no difference in achieving abstinence for different forms of NRT
   - reduces cravings and withdrawal symptoms without other harmful substances contained in cigarettes
   - cost of NRT is comparable, and often lower than cigarettes
   - use with caution: immediately post-MI, worsening angina, arrhythmia
   - advise no smoking while using NRT
   - public reimbursement for smoking cessation treatment varies across Canada – see https://www.helpthemquit.ca/treatment/costs-coverage for more details
2. Antidepressants (mechanism of action appears to be independent of antidepressant effect)
   - bupropion SR (Zyban®)
   - 21% abstinent at 12 mo vs. 8% for placebo
   - bupropion has similar effectiveness to NRT
3. Varenicline (Champix®)
   - partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce response to smoked nicotine)
   - more effective than bupropion (23% abstinent from 9-52 wk with varenicline vs. 16% with bupropion vs. 9% with placebo)
   - significant side effects (including nausea, headache, drowsiness, unusual dreams, neuropsychiatric symptoms) may lower patient compliance

Table 6. Types of Nicotine Replacement Therapy

Type	Dosage	Comment	Side Effects
Nicotine Gum (OTC)	2 mg if <25 cig/d 4 mg if >25 cig/d 1 piece q1-2 h for 1-3 mo (max 24 pieces/d)	Chew until "peppery" taste then "park" between gum and cheek to facilitate absorption Continue to chew/park intermittently for 30 min	Mouth soreness Hiccups Dyspepsia Jaw ache (Most are transient)
Nicotine Patch (OTC)	Use for 8 wk 21 mg/d x 6 wk 14 mg/d x 2 wk 7 mg/d x 2 wk	Start with lower dose if <10 cig/d Change patch q24 h and alternate sides	Skin irritation Insomnia Palpitations Anxiety
Nicotine Inhaler (OTC)	6-16 cartridges/d up to 12 wk	Nicotine inhaled through mouth, absorbed in mouth and throat (not in lungs)	Local irritation Cough
Nicotine Nasal Spray (Rx)		Newer form of NRT	Local irritation Cough

Antidepressants for Smoking Cessation
Cochrane DB Syst Rev 2020;4:CD000031
Purpose: To assess evidence for the efficacy, safety, and tolerability of medications with antidepressant properties in assisting long-term tobacco smoking cessation.
Methods: Meta-analysis of RCTs comparing antidepressant medications to placebo or alternative pharmacotherapy, or the same medication used in a different way for smoking cessation. Safety analyses with any follow-up length was also conducted.
Results: Compared to placebo, bupropion was associated with increased long-term smoking cessation rates (RR 1.64, 95% CI 1.52-1.77), higher risk of reported psychiatric adverse events (RR 1.25, 95% CI 1.15-1.37), and higher dropout rate due to adverse events of the drug (RR 1.37, 95% CI 1.21-1.56). Bupropion resulted in inferior cessation rates to varenicline (RR 0.71, 95% CI 0.64-0.79), however no difference in efficacy between bupropion and NRT was found. Additionally, nortriptyline aided smoking cessation when compared with placebo (RR 2.03, 95% CI 1.48-2.78). There was insufficient evidence to establish whether combination bupropion and NRT resulted in superior quit rates to NRT alone, or whether combination bupropion and varenicline resulted in superior quit rates to varenicline alone.
Conclusion: Evidence suggests that bupropion may be helpful and as successful as NRT and nortriptyline in helping people to quit smoking, but that it is less effective than varenicline.

The 5 A's for Patients Willing to Quit
Ask if the patient currently smokes and is willing to discuss cessation
Advise the patient to quit
Assess willingness to quit
Assist in quit attempt(s)
Arrange follow-up

The 2-3 Pattern of Smoking Cessation
Onset of withdrawal is 2-3 h after last cigarette
Peak withdrawal is at 2-3 d
Expect improvement of withdrawal symptoms at 2-3 wk
Resolution of withdrawal at 2-3 mo
Highest relapse rate within 2-3 mo

Assist Patient in Developing Quit Plan

STAR
Set quit date
Tell family and friends (for support)
Anticipate challenges (e.g. withdrawal)
Remove tobacco-related products (e.g. ashtrays/lighters)

Table 7. Pharmacologic Treatments for Smoking Cessation

Drug	Mechanism	Dosage	Prescribing*	Contraindications
Bupropion	Inhibits re-uptake of dopamine and/or NE Side effects: insomnia, dry mouth	1. 150 mg qAM x 3 d 2. Then 150 mg BID x 7-12 wk 3. For maintenance consider 150 mg BID for up to 6 mo	1. Decide on a quit date 2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk)	Seizure disorder Eating disorder MAOI use in the past 14 d Simultaneous use of bupropion (Wellbutrin®) for depression
Varenicline	Partial nicotinic receptor agonist, and partial competitive antagonist of nicotinic receptor Side effects: nausea, vomiting, constipation, headache, dream disorder, insomnia, increased risk of psychosis, depression, suicidal ideation	1. 0.5 mg qAM x 3 d 2. Then 0.5 mg BID x 4 d 3. Continue 1 mg BID x 12 wk ± additional 12 wk as maintenance	1. Decide on a quit date 2. Continue to smoke for first wk of treatment and then completely stop	Caution with pre-existing psychiatric condition

*Bupropion and varenicline may be used in combination with NRT

- pregnant patients: counselling is recommended as first line treatment
  - NRT should be made available to pregnant women who are unable to quit using non-pharmacologic methods
  - intermittent NRT use (lozenges, gum) is preferred over continuous dosing of the patch
  - no strong evidence that either major positive or negative outcomes were associated with gestational use of bupropion or varenicline; consider using only if benefits outweigh risks
- unwilling to quit
  - motivational intervention (5 Rs)
    1. **R**elevance to patient
       - relevance to patient's disease status or risk, family or social situation (e.g. having children in the home), health concerns, age, gender
    2. **R**isks of smoking
       - short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
       - long-term: MI, stroke, COPD, lung cancer, other cancers
       - environmental: higher risk in spouse/children for lung cancer, SIDS, asthma, respiratory infections
    3. **R**ewards: (benefits)
       - improved health, save money, food tastes better, good example for children
    4. **R**oadblocks: (obstacles)
    fear of withdrawal, weight gain, failure, lack of support
    5. **R**epetition
       - reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)
- recent quitter
  - highest relapse rate within 3 mo of quitting
    - minimal practice: congratulate success, encourage ongoing abstinence, review benefits and risks
    - prescriptive interventions: address problem(s) of weight gain, negative mood, withdrawal, lack of support

Physician Advice for Smoking Cessation
Cochrane DB Syst Rev 2013;5:CD000165
Purpose: To assess the effectiveness of physician advice in promoting smoking cessation, compare minimal physician interventions with more intensive interventions, assess the effectiveness of various aids in smoking cessation, and determine the effect of anti-smoking advice on mortality.
Methods: Systematic review of RCTs of smoking cessation advice from a medical practitioner. Abstinence was assessed ≥6 mo after advice was first provided.
Results: Trials with over 31000 smokers were identified. Most common setting for advice delivery was primary care. A significant increase in quitting rates was noted with advice vs. no advice (RR 1.66, 95% CI 1.42-1.94), which was further increased where the intervention was considered more intensive (RR 1.84, 95% CI 1.60-2.13; n.s.). Intensive advice showed a small, non-significant advantage vs. minimal advice when directly compared (RR 1.37, 95% CI 1.20-1.56). A small benefit with follow-up visits was also noted. No statistically significant difference in mortality at 20 yr follow-up was found.
Conclusion: Simple advice can increase smoking cessation rates by 1-3% on top of the unassisted quit rate. More intensive advice and providing follow-up support may further increase quit rates.

Alcohol Use

- see Psychiatry, PS28

Definition
- alcohol use disorder diagnostic categories occur along a continuum

Epidemiology
- 10-15% of patients in family practice misuse alcohol
- 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
- more likely to miss diagnosis in women, elderly, and patients with high socioeconomic status

Assessment
- screen for alcohol dependence with CAGE questionnaire
  - if CAGE is positive, further explore for the possibility of alcohol misuse or dependence
- assess drinking profile
  - setting, time, place, occasion, with whom
  - impact on family, work, social life
  - quantity-frequency history
    - how many drinks per day?
    - how many days per week?
    - maximum number of drinks on any one day in the past month?
- the Alcohol Use Disorders Identification Test (AUDIT) is another useful tool to assess alcohol use, drinking behaviours, and alcohol-related problems
- if identified positive for alcohol use disorder:
  - screen for other drug use
  - identify any medical/psychiatric complications (e.g. delirium tremens or withdrawal seizures)

Standard Drink Equivalents
- One standard drink = 13.64 g of pure alcohol
- Beer/Cider/Cooler (5% alcohol) = 12 oz
- Malt liquor (7% alcohol) = 8-9 oz
- Wine (12-17% alcohol) = 5 oz
- Fortified wine = 3 oz
- Hard liquor (40%) = 1.5 oz

CAGE Questionnaire
Have you ever felt you needed to Cut down on your drinking?
Have people Annoyed you by criticizing your drinking?
Have you ever felt Guilty about drinking?
Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?
Two "yes" responses is considered positive

- ask about drinking and driving
- ask about past recovery attempts and assess current readiness to change

Investigations
- GGT and MCV for baseline and follow-up monitoring
- AST, ALT (usually AST:ALT approaches 2:1 in persons with alcohol use disorder)
- CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by the liver)

Management
- intervention should be consistent with patient's motivation for change
- individualized counselling and regular follow-up is crucial
- 10% of patients in alcohol withdrawal will have seizures or delirium tremens
- Alcoholics Anonymous/12-step program
  - outpatient/day programs for those with chronic, resistant alcohol use disorder
  - family treatment (Al-Anon, Alateen, screen for spousal/child abuse)
- refer to specialist or inpatient program if:
  - dangerous or highly unstable home environment
  - severe medical/psychiatric concern
  - addiction to drug that may require in-patient detoxification
  - refractory to other treatment programs
- pharmacologic
  - diazepam for withdrawal
  - disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, N/V, hypotension if alcohol is ingested (available in U.S., but no longer available in Canada)
  - naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
    - may trigger withdrawal in opioid-dependent patients
  - acamprosate: glutamate receptor modulator that also reduces craving
- see Psychiatry, PS29

Some Adverse Medical Consequences of Problem Drinking
GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/esophageal cancer
Cardiac: HTN, alcoholic cardiomyopathy
Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
Hematologic: anemia, coagulopathies
Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage

Prognosis
- relapse is common and should not be viewed as failure
- monitor regularly for signs of relapse
- 25-30% of persons with alcohol use disorder exhibit spontaneous improvement over 1 yr
- 60-70% of individuals with jobs and families have improved quality of life 1 yr post-treatment

Common Presenting Problems

Abdominal Pain

- see Gastroenterology, G4, General Surgery and Thoracic Surgery, GS4, and Emergency Medicine, ER18

Epidemiology
- 20% of individuals have experienced abdominal pain within the last 6-12 mo
- 90% resolve in 2-3 wk
- only 10% are referred to specialists, of those <10% admitted to hospital

Etiology
- most common diagnosis in family medicine at 28% is "nonspecific abdominal pain," which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: DKA, porphyria, hypercalcemia, medications (e.g. NSAIDs), alcohol, toxic ingestion, foreign body, psychogenic

Pathophysiology
- type of pain
  - somatic pain: sharp, localized pain
  - visceral pain: dull, generalized pain
- location of pain
  - epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
    - right upper quadrant (RUQ): biliary, hepatic, colonic, pulmonary, renal
    - left upper quadrant (LUQ): cardiac, gastric, pancreatic, renal, vascular
  - periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon
  - hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region
    - right lower quadrant (RLQ): colonic, appendix, gynecological, renal
    - left lower quadrant (LLQ): colonic, gynecological, renal
  - any location: aneurysm, dissection, ischemia, varicella zoster virus, muscle strain, hernia, bowel obstruction, peritonitis, porphyria, DKA

If pain precedes nausea/vomiting, cause of abdominal pain is more likely to require surgery

Abdominal Pain Red Flags
- Severe pain
- Signs of shock
- Peritoneal signs
- Abdominal distention
- Pain out of proportion to clinical findings
- New onset pain, change in pain, or altered bowel habits in elderly
- Weight loss
- Blood per rectum/melena
- Anemia
- Supraclavicular lymph nodes
- Family history of serious bowel disease

In patients >50, keep a high index of suspicion for AAA – its presentation may mimic renal colic or diverticulitis

Investigations
- guided by findings on history and physical
- possible blood work: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, toxicology screen, β-hCG
- imaging
  - CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  - AXR, KUB (consider: gas pattern, free air, kidney stones, constipation)
  - U/S (renal stones, gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  - CT-scan (AAA, appendicitis), non-contrast helical CT-scan (first choice for renal stones)
- other tests
  - urinalysis
  - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
  - *H. pylori* testing (urea breath test, serology, biopsy)

Allergic Rhinitis

- see Otolaryngology, OT24

Differential Diagnosis
Acute viral infection
Vasomotor rhinitis
Deviated septum
Nasal polyps
Acute/chronic sinusitis
Drug-induced rhinitis

Rhinitis Medicamentosa
Rebound nasal congestion. Occurs with prolonged use (>5-7 d) of vasoconstrictive intranasal medications. Patient may become dependent, requiring more frequent dosing to achieve the same decongestant effect

Definition
- inflammation of the nasal mucosa that is triggered by an allergic reaction
- classification
  - seasonal
    - symptoms during a specific time of the year
    - common allergens: trees, grass, and weed pollens, airborne moulds
  - perennial
    - symptoms throughout the year with variation in severity
    - common allergens: dust mites, animal dander, moulds
- persistent allergic rhinitis may lead to chronic rhinosinusitis

Epidemiology
- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, eczema, sinusitis, and otitis media

Etiology
- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

Assessment
- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

Management
- conservative
  - minimize exposure to allergens
    - most important aspect of management, often sufficient (may take months)
  - maintain hygiene, saline nasal rinses
- pharmacologic agents
  - oral second-generation antihistamines – first-line therapy for mild symptoms
    - e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  - intranasal corticosteroids for moderate/severe or persistent symptoms (expect >1 mo of consistent use to see results)
  - intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)
- allergy skin testing
  - for patients with chronic rhinitis whose symptoms are not controlled by conservative and pharmacological therapy
  - may identify allergens to include in immunotherapy treatment
- immunotherapy (allergy shots)
  - reserved for severe cases unresponsive to pharmacologic agents
  - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

Amenorrhea

- see Gynecology, GY9
- absence of menses due to dysfunction of the hypothalamus, pituitary, ovaries, uterus, and/or vagina. Classified as either primary (absence of menarche by age 15 or thereafter) or secondary (absence of menses >3 mo in women who previously had regular menstrual cycles)

Anxiety

• see Psychiatry, PS16

Epidemiology

- 25-30% of patients in primary care settings have psychiatric disorders
- many are undiagnosed or untreated; hence the need for good screening
- high rate of coexistence of anxiety disorders and depression

Screening

- screening tools such as the GAD-7 tool
- screening questions
  - do you tend to be an anxious or nervous person?
  - have you felt unusually worried about things recently?
  - has this worrying affected your life? How?

Assessment

- identify associated symptoms on history and physical to rule out organic medical causes (e.g. hyperthyroidism, cardiopulmonary disorder, traumatic brain injury)
- risk factors: past history of anxiety, stressful life event, trauma, social isolation, female , LGBTQ2S+, comorbid psychiatric diagnosis (e.g. depression), family history of anxiety or depression
- assess substance misuse, suicidal ideation/self-harm
- to differentiate anxiety disorders, consider symptoms and their duration
- use the GAD-7 tool to assess and monitor levels of anxiety
- ask patients about experiences that may impact current situation and intersectionality

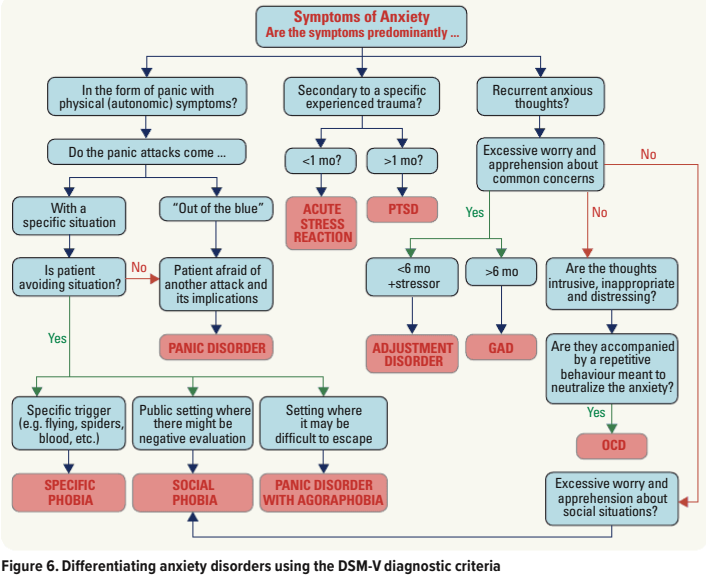

Symptoms of Anxiety
Are the symptoms predominantly ...
In the form of panic with physical (autonomic) symptoms?
Secondary to a specific experienced trauma?
Recurrent anxious thoughts?
Do the panic attacks come ...
<1 mo?
>1 mo?
Excessive worry and apprehension about common concerns
No
With a specific situation
"Out of the blue"
ACUTE STRESS REACTION
PTSD
Yes
No
Is patient avoiding situation?
No
Patient afraid of another attack and its implications
<6 mo +stressor
>6 mo
Are the thoughts intrusive, inappropriate and distressing?
Yes
PANIC DISORDER
ADJUSTMENT DISORDER
GAD
Are they accompanied by a repetitive behaviour meant to neutralize the anxiety?
Yes
Specific trigger (e.g. flying, spiders, blood, etc.)
Public setting where there might be negative evaluation
Setting where it may be difficult to escape
OCD
SPECIFIC PHOBIA
SOCIAL PHOBIA
PANIC DISORDER WITH AGORAPHOBIA
Excessive worry and apprehension about social situations?

Figure 6. Differentiating anxiety disorders using the DSM-V diagnostic criteria
Adapted from: Evans M, Bradwejn J, Dunn L. Anxiety Review Panel. Guidelines for the treatment of anxiety disorders in primary care. Toronto: Queen's Printer of Ontario, 2000.41

Management

- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- with consent, explore lifestyle habits: exercise, caffeine, alcohol intake, etc. and collaboratively develop a person-centered plan (e.g. reduce caffeine at a particular pace)
- psychological: psychotherapy including CBT, exposure therapy, relaxation techniques, and mindfulness strategies
- pharmacotherapy: see Psychiatry, PS50
- offer self-help materials, connect with community resources (e.g. support groups), and provide support to family and caregivers

Differential Diagnosis of Anxiety Disorders
- Panic disorder
- GAD
- Social anxiety disorder (previously social phobia)
- Agoraphobia
- Specific phobia
- Selective mutism
- Separation anxiety disorder
- Other: general medical condition, AMC, mood disorder, psychotic disorder, OCD, PTSD

Symptoms of GAD

AND I C REST
Anxious, nervous, or worried
No control over the worry
Duration >6 mo
Irritability
Concentration impairment
Restlessness
Energy decreased
Sleep impairment
Tension in muscles
Can Fam Physician 2005;51:1340-42

Rule Out
- Cardiac (post MI, arrhythmias)
- Endocrine (hyperthyroidism, diabetes, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatoform disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (OCPD, avoidant personality disorder)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/benzodiazepine withdrawal)

Differential Diagnosis of Wheezing
- Allergies, anaphylaxis
- Asthma, reactive airway disease
- GERD
- Infections (bronchitis, pneumonia)
- OSA
- COPD
- Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction

Self-Management Asthma and COPD Education and Written Action Plan

Education is a key component in management of asthma and COPD

Guided self-management combining education, regular medical review, self-assessment, and written action plans have been shown to reduce hospitalizations, ED visits, and missed days at work or school

Sample action plans available online: https://cts-sct.ca/

Asthma/COPD

- see Respirology, R7

Definition

- asthma
  - chronic, reversible airway inflammation characterized by periodic attacks of wheezing, dyspnea, chest tightness, and coughing
  - airways are hyper-responsive to triggers/antigens leading to acute obstructive symptoms including bronchoconstriction, mucous plugs, and increased inflammation
  - cannot be diagnosed at first presentation
  - PFTs can be done starting at age 6 or when child is able to follow testing instructions
  - peak flow metres are useful in the office and at home for monitoring
- COPD
  - group of chronic, progressive, non-reversible lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
  - emphysema and chronic bronchitis are the most common forms

Table 8. Differentiating COPD from Asthma

	COPD	Asthma
Age of Onset	Usually in 6th decade	Any age (but 50% of cases are diagnosed in children ages <10)
Role of Smoking	>10 pack yr	Not causal, known trigger
Reversibility of Airflow Obstruction	Airflow obstruction is chronic and persistent	Airflow obstruction is episodic and usually reversible with therapy
Evolution	Slow, progressive worsening (with periodic exacerbations)	Stable, episodic, <50% will outgrow
History of Allergy	Infrequent	>50% patients
Precipitators	Environmental irritants (air pollution), cigarette smoking, α-1 antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs)	Environmental irritants (dust, pollen), animal fur, cold air, exercise, URTIs, cigarette smoke, use of β-blockers/ASA
Symptoms/Signs	Chronic cough, sputum, and/or dyspnea	Wheeze (hallmark symptom), dyspnea, chest tightness, prolonged expiration, cough which is worse in the cold, at night, and in the early AM
Diffusion Capacity	Decreased (more so in pure emphysema)	Normal (for pure asthma)
Hypoxemia	Chronic in advanced stages	Not usually present Episodic with severe attacks
Spirometry	May have improvement with bronchodilators but not universally seen	Marked improvement with bronchodilators or steroids
Chest X-Ray	Often normal Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist, bullae	Often normal or episodic hyperinflation Hyperinflation during asthma attack
Management	**All: Smoking Cessation** **Mild** Step 1: SABA as needed (salbutamol) Step 2: SABA as needed + LAAC (i.e. tiotropium) or + LABA (e.g. salmeterol) **Moderate** Step 3: SABA/SAMA + LABA or SABA + LABA or LAAC; consider inhaled vs. oral steroids **Severe** Step 4: Pneumococcal vaccination, annual influenza immunization	Ongoing patient education, and environmental control SABA taken PRN as rescue medication + maintenance meds Maintenance medications **Mild** Step 1: Low-dose ICS Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LTRA modifier **Moderate** Step 3: Medium/high-dose ICS + either LABA, LT modifier **Severe** Step 4: As above + immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization

ICS = inhaled corticosteroids; LAAC = long-acting anticholinergic; LABA = long-acting β-agonist; LT modifier = leukotriene modifier; SABA = short-acting β-agonist, SAMA = short acting muscarinic antagonist

Signs of Poorly Controlled Asthma
β2-agonist use >4x/wk
Asthma-related absence from work/school
Exercise-induced asthma
Night-time symptoms >1x/wk

What Colour is Your Inhaler?

Name	Body/Cap Colour
β2-Agonists	
salbutamol – Ventolin®	Light blue/navy
salmeterol – Serevent®	Teal/light teal
terbutaline – Bricanyl®	Blue/white
ICS	
fluticasone – Flovent®	Orange/peach
budesonide – Pulmicort®	White/brown
Combined Long-Acting β2-Agonist + ICS	
fluticasone/salmeterol – Advair®	Purple discus
budesonide/formoterol–Symbicort®	Red/white
fluticasone/ vilanterol– Breo®	Grey/blue
Anticholinergics	
umeclidinium - Incruse®	White/green
ipratropium – Atrovent®	Clear/green
tiotropium – Spiriva®	White/turquoise

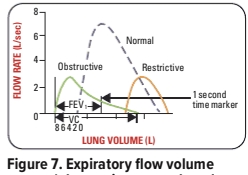


Figure 7. Expiratory flow volume curves (obstructive, normal, and restrictive disease) See Respirology, R4
Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. With permission from Elsevier. ©2008

More About Inhalers
- Aerosols (puffers = MDI, MDI + spacer) MDIs should be used with spacers to:
- Reduce side effects
- Improve amount inhaled
- Increase efficiency of use
- DPI (discuss, turbuhaler, and diskhaler) require deep and fast breathing (may not be ideal for children)
- Nebulizers can be used to convert liquid medications into a fine mist: recommended for use if contraindications to MDIs
- Currently there is large push in clinical practice to transition away from the use of MDI and to move towards using DPI to reduce the impact of aerosol treatments on the environment - Evohaler MDIs had 20–30 times larger carbon footprints than the Accuhaler and Elipta DPIs (Thorax 2020 Jan;75(1):82-84.)

When prescribing salbutamol, watch out for signs of **hypokalemia**: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, N/V, polyuria

Benign Prostatic Hyperplasia

• see Urology, U7

Definition
• hyperplasia of the stroma and epithelium in the periurethral transition zone

History and Physical
• include current/past health, surgeries, trauma, current medications including OTC
• specific urinary symptoms
• physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth, and rubbery in BPH)

Investigations
• urinalysis to exclude UTI and for microscopic hematuria (common sign)
• serum PSA: protein produced by prostatic tissue
  - PSA to screen/test for BPH is no longer used due to the high false positive rate, and is instead used as a marker to guide treatment once diagnosis has been made
  - PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI
  - increased PSA in a younger man is more often due to cancer than other causes
  - abnormal DRE or PSA should trigger further assessment
  - discuss test with men at increased risk of prostate cancer (FMHx, Black men) or who are concerned about development of prostate cancer
  - decision to test PSA in an asymptomatic man (see *Prostate Cancer Screening, FM6*)
• other tests
  - Cr, BUN, PVR volume by U/S, urodynamic studies, renal U/S, patient voiding diary
• tests NOT recommended as part of routine initial evaluation include:
  - cystoscopy, cytology, prostate U/S or biopsy, IVP, urodynamic studies

Table 9. Symptoms and Complications of BPH

Obstructive Symptoms	Irritative Symptoms	Late Complications
Hesitancy (difficulty starting urine flow)	Urgency	Hydronephrosis
Diminution in size and force of urinary stream	Frequency	Loss of renal concentrating ability
Stream interruption (double voiding)	Nocturia	Systemic acidosis
Urinary retention (bladder does not feel completely empty)	Urge incontinence	Renal failure
Post-void dribbling	Dysuria	
Overflow incontinence		
Nocturia		

Management
• referral to urologist if moderate/severe symptoms
• conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
  - fluid restriction (avoid alcohol and caffeine)
  - avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
  - pelvic floor/Kegel exercises; consider referral to pelvic physiotherapist
  - bladder retraining (scheduled voiding)
• pharmacological: for moderate/severe symptoms
  - α-receptor antagonists (e.g. terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), alfuzosin (Xatral®))
    - relax smooth muscle around the prostate and bladder neck
  - 5-α reductase inhibitors (e.g. finasteride (Proscar®))
    - only for patients with demonstrated prostatic enlargement due to BPH
    - inhibit the enzyme responsible for conversion of testosterone to dihydrotestosterone thus reducing growth of prostate
  - antimuscarinic and β-3 agonists
    - recommended for storage symptoms, but avoid in patients with bladder outlet obstruction and/or elevated PVR
  - long-acting phosphodiesterase inhibitor
    - recommended in patients with erectile dysfunction
  - desmopressin
    - recommended for nocturia as a result of nocturnal polyuria (watch for hyponatremia in older adults)
• surgical
  - TURP , TUIP (for prostate <30 g)
  - absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
  - complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido

Bronchitis (Acute)

Definition
- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

Epidemiology
- 5th most common diagnosis in family medicine, and most common is URTI

Etiology
- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, and RSV
- 20% bacterial: *M. pneumoniae, C. pneumoniae*, and *S. pneumoniae*

Investigations
- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not useful
- CXR if suspecting pneumonia (cough >3 wk, abnormal vital signs, localized chest findings) or HF
- PFT with methacholine challenge if suspecting asthma

Management
- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/d when febrile), humidity, analgesics, and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
  - antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic (see *Antimicrobial Quick Reference, FM54*)
  - antibiotics in children show no benefit

Differential Diagnosis of Bronchitis
- URTI
- Asthma
- Acute exacerbation of chronic bronchitis
- Sinusitis
- Pneumonia
- Bronchiolitis
- Pertussis
- Environmental/occupational exposures
- Post-nasal drip
- Others: GERD, CHF, cancer, aspiration syndromes, CF, foreign body

How to Tell if Viral or Bacterial?
Bacterial infections tend to give a higher fever, excessive amounts of purulent sputum production, and may be associated with concomitant COPD

Chest Pain

- see Cardiology and Cardiac Surgery, C5 and Emergency Medicine, ER21

Differential Diagnosis

Table 10. Differential Diagnosis of Chest Pain

Diagnosis	Clinical Findings	LR+	LR−
Acute MI	Chest pain radiates to both arms	7.1	0.67
	Third heart sound on auscultation	3.2	0.88
	Hypotension	3.1	0.96
Chest Wall Pain	>2 of: localized muscle tension, stinging pain, pain reproducible by palpation, absence of cough	3.0	0.47
GERD	Burning retrosternal pain, acid regurgitation, sour or bitter taste in the mouth; 1 wk trial of high-dose proton pump inhibitor relieves symptoms	3.1	0.30
Panic Disorder/Anxiety State	Single question: In the past 4 wk, have you had an anxiety attack (suddenly feeling fear or panic)?	4.2	0.09
Pericarditis	Clinical triad of pleuritic chest pain (increases with inspiration or when reclining, and is lessened by leaning forward), pericardial friction rub, and electrocardiographic changes (diffuse ST segment elevation and PR interval depression without T wave inversion)	N/A	N/A
Pneumonia	Egophony	8.6	0.96
	Dullness to percussion	4.3	0.79
	Fever	2.1	0.71
	Clinical impression	2.0	0.24
Heart Failure	Pulmonary edema on chest radiography	11.0	0.48
	Clinical impression	9.9	0.65
	History of heart failure	5.8	0.45
	History of acute myocardial infarction	3.1	0.69
Pulmonary Embolism	High pretest probability based on Wells criteria	6.8	1.8
	Moderate pretest probability based on Wells criteria	1.3	0.7
	Low pretest probability based on Wells criteria	0.1	7.6
Acute Thoracic Aortic Dissection	Acute chest or back pain and a pulse differential in the upper extremities	5.3	N/A

Adapted from: McConaghy J, Rupal S. Outpatient diagnosis of acute chest pain in adults. Am Fam Physician. 2013 Feb 1; 87(3): 177.182

Risk Factors for CAD
- Major
- Smoking
- Diabetes
- HTN
- Hyperlipidemia
- Family history of early CAD in first degree relative (males <55 yr, females <65 yr)
- Untreated OSA
- CKD

Minor
- Obesity
- Sedentary lifestyle
- Age

Red Flags
- Severe pain
- Pain for >20 min
- New onset pain at rest
- Severe SOB
- Loss of consciousness
- Hypotension
- Tachycardia
- Bradycardia
- Cyanosis

MI in Elderly Women
Elderly women can often present with dizziness, back pain, lightheadedness, or weakness in the absence of chest pain

MI in Diabetics
May present with dyspnea, syncope, and fatigue in the absence of chest pain

Investigations
- ECG, CXR, and others if indicated (cardiac enzymes, d-dimer, LFTs, etc.)
- refer to ED if suspecting serious etiology (e.g. aortic dissection, MI)

Management of Common Causes of Chest Pain
- angina/ischemic heart disease
  - NTG: wait 5 min between sprays and if no effect after 3 sprays, send to ED
- MI
  - ASA (160-325 mg, chewed STAT), clopidogrel (Plavix®) or ticagrelor (Brilinta®), LMWH (enoxaparin), morphine, oxygen, NTG
  - ± reperfusion therapy with fibrinolytics (e.g. tissue plasminogen activator (tPA), reteplase (rPA), tenecteplase (TNK), or streptokinase (SK)) if within 12 h (ideally <30 min) or time from first medical contact to percutaneous intervention (catheter lab) if <30 min
  - start β-blocker (e.g. metoprolol starting dose 25 mg PO q6h or BID, titrating to HR goal of 55-60 bpm)
- endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results
- GERD: antacids, H2-blockers, PPIs, patient education
- costochondritis: NSAIDs

Ruling Out CAD in Primary Care
CMAJ 2010;182(12):1295-1300
Components of the prediction rule used to determine the presence or absence of CAD in patients with chest pain in primary care:
- Age/sex (female ≥65, male ≥55): 1 pt
- Known clinical vascular disease (coronary artery disease, occlusive vascular disease, or cerebrovascular disease): 1 pt
- Pain worse during exercise: 1 pt
- Pain not reproducible by palpation: 1 pt
- Patient assumes pain is of cardiac origin: 1 pt

Positive result: 3-5 pts; negative result: ≤2 pts (sensitivity: 87.1%, specificity: 80%)

Common Cold (Acute Rhinitis)

- see Infectious Diseases, *Pneumonia*, ID7 and *Influenza*, ID9

Definition
- viral URTI with inflammation

Epidemiology
- most common diagnosis in family medicine, peaks in winter months
- incidence: adults = 2-4/yr, children = 6-10/yr
- organisms
  - mainly rhinoviruses (30-35% of all colds)
  - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
- incubation: 1-5 d
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

Risk Factors
- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

Clinical Features
- symptoms
  - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
  - general: malaise, headache, myalgias, mild fever
- signs
  - erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam
- complications
  - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
  - asthma/COPD exacerbation

Differential Diagnosis
- allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

Management
- patient education
  - symptoms peak at 1-3 d and usually subside within 1 wk
  - cough may persist for days to weeks after other symptoms disappear
  - no antibiotics indicated because of viral etiology
  - secondary bacterial infection can present within 3-10 d after onset of cold symptoms
- prevention
  - frequent hand washing, avoidance of hand to mucous membrane contact, use of surface disinfectant
  - yearly influenza vaccination
- symptomatic relief
  - rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
  - analgesics and antipyretics: acetaminophen, ibuprofen
  - cough suppression: dextromethorphan or codeine if necessary (age <6 should not use any cough/cold medications)
  - decongestants, antihistamines
- patients with asthma will require increased use of bronchodilators and inhaled steroids

Influenza vs. Colds: A Guide to Symptoms

Features	Flu	Cold
Onset of illness	Sudden	Slow
Fever	High fever	None
Exhaustion level	Severe	Mild
Cough	Dry severe or hacking	±
Throat	Fine	Sore
Nose	Dry and clear	Runny
Head	Achy	Headache-free
Appetite	Decreased	Normal
Muscles	Achy	Fine
Chills	Yes	No

Echinacea for Preventing and Treating the Common Cold
Cochrane DB Syst Rev 2014;2:CD000530
Purpose: To assess whether echinacea preparations are effective and safe for the prevention and treatment of the common cold.
Methods: Meta-analysis of RCTs comparing mono-preparations of echinacea with placebo. Primary efficacy outcome was number of individuals with at least one cold in prevention trials and duration of colds in treatment trials. Primary safety and acceptability outcome was the number of participants dropping out due to adverse events.
Results: Twenty-four double-blind trials with 4631 participants were included. No prevention study comparisons comparing echinacea and placebo found a statistically significant difference in terms of number of patients with at least one cold episode, though a relative risk reduction of 10% to 20% was identified. Of treatment trials reporting on duration of colds, only 1 study of 7 showed a significant effect favouring echinacea over placebo. No significant differences were found between echinacea and placebo groups in number of dropouts due to adverse events, though prevention trials showed a trend towards higher dropout numbers due to adverse events in treatment groups.
Conclusions: Echinacea products have not been shown to provide benefits for treating colds, although it is possible there is a weak benefit from some echinacea products. Individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance.

Concussion/Mild Traumatic Brain Injury

- see Neurosurgery, NS36 and Emergency Medicine, ER7
- a useful tool for the assessment of individuals and athletes with concussion is the Sport Concussion Assessment Tool, 5th edition (SCAT5), Br J Sports Med 2017;0:1-8
- Parachute Canada concussion guidelines including return to play/return to sports: https://parachute.ca/en/injury-topic/concussion/

Contraception

- see Gynecology, GY15

Emergency Contraception

- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 h apart) or post-coital copper IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
- copper IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
- pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
- advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
- pharmacists across Canada can dispense Plan B® OTC

Cough

History and Physical

- duration (chronic ≥8 wk), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptysis, wheezing, chest pain, orthopnea, PND, rhinitis, reflux, post-nasal drip
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, environmental allergies, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (e.g. ACEI, β-blockers), allergies
- PMHx: lung (asthma, COPD, CF), heart (HF, MI, arrhythmias), chronic illness, GI (reflux)
- vitals including O_2 saturation, respiratory exam, HEENT, and precordial exam

Investigations

- guided by findings on history and physical
  - CXR, PFTs, upper GI series, sputum culture test for acid-fast bacilli (if TB is suspected)

Differential Diagnosis

Common Causes

Upper airway cough syndrome (post-nasal drip)
Asthma/COPD
GERD
Non-asthmatic eosinophilic bronchitis

Other Causes

- ACEI
- Aspiration
- Bronchiectasis
- Cystic fibrosis
- Chronic interstitial lung disease
- CHF
- Lung/laryngeal cancer
- Pertussis
- Psychogenic
- Restrictive lung disease
- TB, atypical mycobacterium, and other chronic lung infections

Dementia (Major Neurocognitive Disorder)

- see Psychiatry, PS24

Epidemiology

- 15% of Canadians ≥65 yr are living with dementia; risk for dementia doubles every 5 yr after age 65
- prevalence of depression in dementia is 20-60%; major depression decreases as dementia severity increases; vascular and mixed dementias have a higher prevalence of depression
- leading types of dementia: Alzheimer's (40-50%), mixed (20-25%), Lewy-Body (5-15%), vascular (5-10%), frontotemporal (5-10%)

Investigations

- history, physical exam, MMSE, MOCA (best screening test), Dementia Quick Screen (see sidebar)
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin B12, folate, VDRL, HIV, head CT

Management

- treat and prevent reversible causes
- provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
- family education, counselling, and supports (alternative levels of care)
- pharmacologic therapy: N-methyl-d-aspartate receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose antipsychotics and antidepressants can be used to treat behavioural and emotional symptoms
- 20% of patients develop clinical depression, most commonly seen in vascular dementia

Dementia Quick Screen = Mini Cog + Animal Naming

- 3 simple tests, takes about 2 min
- Use when suspecting mild cognitive impairment or when patient is at high-risk
- Mini Cog = 3 words recalled + clock drawing
  - Clock Drawing – including numbers and hands so time shows 10 min past 11 (normal = correct number/hand placing or only minor spacing problems)
  - 0 word recall = impairment
  - 1-2 words and clock drawing abnormal = impairment
  - 3 words recalled = normal
  - Naming animals in 1 min (normal = >15 in 1 min)
- Interpretation: If all 3 results within normal range, cognitive impairment unlikely
- Return for further evaluation if:
  - <15 animals named
  - 0-1 words recalled
  - Clock drawing abnormal

Depression

• see Psychiatry, PS12

Etiology

- often presents as non-specific complaints (e.g. sleep disturbance, chronic fatigue, pain); can be associated with triggers (e.g. major life events)
- depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of patients may not receive appropriate treatment for their depression
- early diagnosis and treatment improve outcomes

Screening Questions

- Canadian Task Force on Preventive Health Care (2013) recommends not routinely screening for depression
- if screening indicated, use the PHQ-2
  - "Over the past 2 wk, how often have you been bothered by any of the following problems":
    - little interest or pleasure in doing things?
    - feeling down, depressed, or hopeless?
- the PHQ-2 is scored out of 6, with a score of 3 or more considered positive
  - those who screen positive should be evaluated with the PHQ-9 to determine whether they meet criteria for depression
- PHQ-9 tool is useful to diagnose and monitor depression; use GDS for the geriatric population
- screen all patients presenting with depression for suicidal ideation and behaviour, a positive screen should prompt additional questioning

Assessment

- risk factors: see Psychiatry, PS12
- personal or family history of depression
- medications and potential substance misuse concerns
- high-risk for suicide/homicide
  - fill out Form 1 (in Ontario): application by physician to hospitalize a patient against their will for psychiatric assessment (up to 72 h)
- functional impairment (e.g. work, relationships)
- at least 5 out of 9 criteria including at least one of anhedonia or depressed mood ≥2 wk for actual diagnosis to be met (see Memory Aid)
- validated depression rating scales: Beck's Depression Inventory, Zung's self-rating depression scale, Children's Depression Inventory, GDS, PHQ-9
- routine medical workup (physical exam, CBC, TSH, ferritin, folate, B12, electrolytes, urinalysis, glucose, etc.)

Treatment

- goal: full remission of symptoms and return to baseline psychosocial function
- phases of treatment
  - acute phase (8-12 wk): relieve symptoms and improve quality of life, counsel patients on risks (e.g. sexual side effects, discontinuation syndrome)
  - maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
- treatment options are pharmacotherapy, psychotherapy, or a combination of both
  - combination therapy is synergistic and most effective (see EBM in sidebar)
- treatment of youth (ages 10-21)
  - for mild depression, a period of active support and monitoring before initiating treatment is recommended
  - fluoxetine is first line among SSRIs (most evidence)
    - monitor closely for adverse effects such as suicidal ideation and behaviour
  - psychotherapy
    - CBT or IPT alone can be used for mild depression
    - psychotherapy plus medication is recommended for moderate to severe depression
  - treatment should continue for at least 6 mo
    - ongoing management should include assessment in key domains (school, home, social setting)
    - reassessment and referral is recommended if there is no improvement after 6-8 wk of treatment
    - consider referral for adolescents with moderate/severe depression and coexisting psychosis and/or substance misuse

Must Ask About/Rule Out

- Suicidal/homicidal ideation
- Psychosis
- Substance use/misuse/withdrawal
- Anxiety
- Bipolar/manic/hypomanic episodes
- Bereavement
- Intimate partner violence
- Postpartum depression
- Organic cause

Differential Diagnosis

- Other psychiatric disorders (e.g. anxiety, personality, bipolar, adjustment disorder, schizoaffective, seasonal affective disorder, substance misuse/withdrawal)
- Cancer (50% of patients with tumours, especially of brain, lung, and pancreas, develop symptoms of depression before the diagnosis of cancer is made)
- Chronic fatigue syndrome
- Early dementia
- Endocrine (e.g. hyper/hypothyroidism, DM, adrenal disorders)
- Infections (mononucleosis)
- Liver failure, renal failure
- Medication side effects (β-blockers, benzodiazepines, glucocorticoids, interferon)
- Menopause
- Neurological (Parkinson's disease, MS)
- Vitamin deficiency (pernicious anemia, pellagra)

Combined Pharmacotherapy and Psychological Treatment for Depression: A Systematic Review
Arch Gen Psychiatry 2004;61:714-719

Purpose: To examine the relationship between adherence and efficacy of antidepressant medications plus psychological treatment vs. medications alone in the management of depressive disorders.

Methods: Systematic review of RCTs comparing antidepressant medications alone vs. combination therapy with psychological intervention included. Efficacy and adherence to therapy were the main outcomes.

Results: Sixteen trials with 1842 patients were included. Patients receiving combination therapy showed significantly greater improvements than those receiving medications alone (OR 1.86, 95% CI 1.38-2.52); dropout and non-responder proportions did not differ in distribution between the two groups (OR 0.86, 0.60-1.24). A significant advantage with combination therapy was noted in studies with follow-up longer than 12 wk (OR 2.21, 1.22-4.03), accompanied by significant reduction in dropout and non-responder proportions.

Conclusion: Combination therapy with psychological treatment and medication is associated with greater improvement rates than medication alone, and may decrease dropout rates with longer therapies.

Table 11. Common Medications

Class	Examples	Action	Side Effects	Notes
SSRI	paroxetine (Paxil®) fluoxetine (Prozac®) sertraline (Zoloft®) citalopram (Celexa®) fluvoxamine (Luvox®) escitalopram (Cipralex®) vortioxetine (Trintellix®)	Block serotonin reuptake	Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase QT interval (baseline ECG is suggested)	First line therapy for youth is fluoxetine; paroxetine is not recommended for youth (controversial)
SNRI	venlafaxine (Effexor®) duloxetine (Cymbalta®) desvenlafaxine (Pristiq®)	Block serotonin and NE reuptake	Insomnia, tremors, tachycardia, sweating	
SDRI	bupropion (Wellbutrin®)	Block dopamine and NE reuptake	Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs	Often chosen for lack of sexual side effects, can be used for augmentation of antidepressant effects with other classes of medication
TCA	amitriptyline (Elavil®)	Block serotonin and NE reuptake	Sexual dysfunction, weight gain, tremors, tachycardia, sweating	Narrow therapeutic window, lethal in overdose

Criteria for Depression
(≥5/9 with at least one of anhedonia or depressed mood for ≥2 wk)

M-SIGECAPS
MDepressed **M**ood
SIncreased/decreased **S**leep
IDecreased **I**nterest
G **G**uilt
EDecreased **E**nergy
CDecreased **C**oncentration
A Increased/decreased Appetite and weight
P **P**sychomotor agitation/retardation
S **S**uicidal ideation

Prognosis
- up to 40% resolve spontaneously within 6-12 mo
- risks of recurrence: 50% after 1 episode, 70% after 2 episodes, 90% after 3 episodes

Diabetes Mellitus

- see Endocrinology, E7
- see 2018 Clinical Practice Guidelines from Diabetes Canada, available from: http://guidelines.diabetes.ca/cpg
- see 2022 Special Article: Remission of Type 2 Diabetes from Diabetes Canada, available from: http://guidelines.diabetes.ca/cpg
- see Diabetes Mellitus Patient Care Flow Sheet from Canadian Diabetes Association, available from: https://guidelines.diabetes.ca/docs/cpg/Appendix-3.pdf

DM Related Symptoms
Hyperglycemia: polyphagia, polydipsia, polyuria, weight change, blurry vision, yeast infections
Diabetic Ketoacidosis (DKA): fruit breath, anorexia, N/V, fatigue, abdominal pain, Kussmaul breathing, dehydration
Hypoglycemia: hunger, anxiety, tremors, palpitations, sweating, headache, fatigue, confusion, seizures, coma

Definition
- metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both

Classification and Diagnosis
- see Endocrinology, E8

Epidemiology
- major health concern, affecting up to 10% of Canadians
- incidence of T2DM is rising due to increasing obesity, sedentary lifestyle, and age of the population
- leading cause of new-onset blindness and renal dysfunction
- Canadian adults with DM are twice as likely to die prematurely compared to persons without DM
- 1 in 5 Indigenous people in Canada has diabetes

Long-Term Complications of DM
Microvascular: nephropathy, retinopathy, neuropathy
- **Macrovascular**: CAD, CVD, PVD

Risk Factors
- T1DM
  - personal or family history of autoimmune disease
- T2DM
  - first degree relative with DM
  - ages ≥40 yr
  - obesity (especially abdominal), HTN, hyperlipidemia, CAD, vascular disease
  - prior gestational diabetes mellitus, macrosomic baby (>4 kg)
  - PCOS
  - history of IGT or IFG
  - presence of complications associated with DM
  - presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  - medications: glucocorticoids, atypical antipsychotics, HAART
- both
  - member of a high-risk population (e.g. Indigenous peoples, Hispanic, Asian, or African descent)

Screening
- T2DM
  - FBG or HbA1c in everyone ≥40 q3 yr, or at high-risk using the CANRISK calculator
  - more frequent and/or earlier testing if presence of ≥1 risk factor (see above)
- gestational diabetes mellitus (see Obstetrics, OB28)
  - all pregnant women between 24-28 wk gestation

A1C Interpretation
- advantages:
  - convenient (measure any time of day)
  - single sample

- predicts microvascular complications
- better predictor of CVD than FBG or two hour plasma glucose in a 75 g OGTT
- slow day-to-day variability
- reflects long-term glucose concentration

• disadvantages:
- cost
- misleading in various medical conditions (e.g. hemoglobinopathies, iron deficiency, hemolytic anemia, severe hepatic or renal disease)
- altered by ethnicity and aging
- standardized, validated assay required
- not for diagnostic use in children and adolescents (as the sole diagnostic test), pregnant women as part of routine screening for gestational diabetes, those with CF, or those with suspected T1DM

Goals of Therapy

• see Endocrinology, E9 and Clinical Pearl (SMART Goals)

Assessment and Monitoring

Table 12. Assessment and Monitoring

	Initial Assessment	q2-4mo	Annually
History	Symptoms of hyperglycemia, ketoacidosis, hypoglycemia Past medical history Functional inquiry Family history Risk factors Medications Sexual function Lifestyle	DM-directed history Screen for awareness and frequency of hypoglycemia and DKA Glucose monitoring Use of insulin and oral agents Smoking cessation	DM-directed history Screen for awareness and frequency of hypoglycemia and DKA Glucose monitoring Use of insulin and oral agents Sexual function Lifestyle counselling Screen for depression
Physical Exam	General: height, weight, BMI, BP, WC Head and neck: fundoscopy, thyroid exam Cardiovascular exam: signs of PVD, pulses, bruits Abdominal exam (e.g. for organomegaly) Hand/foot/skin exam Neurological exam	Wt, BP, BMI, WC	Foot exam for sensation (using a 10 g monofilament), ulcers or infection Remainder of exam as per PHE
Investigations	FBG, HbA1c, fasting lipids, Cr, urine ACR Baseline ECG; repeat testing q2 yr for those at high-risk	HbA1c q3 mo FBG as needed	Fasting lipid profile Annual random urine ACR and Cr
Management	Nutritional and physical education Consider referral to DM education program if available Monitoring blood glucose: explain methods and frequency Medication counselling: oral hypoglycemic agents and/or insulin, method of administration, dosage adjustments Pneumococcal vaccination Ophthalmology consult (T1DM within 5 yr T2DM at diagnosis)	Assess progress towards long-term complications Adjust treatment plan if necessary	Calibrate home glucose monitor Arrange annual retinopathy screening Influenza vaccination annually

Nonpharmacologic Management

• diet
- can reduce HbA1c by 1-2%
- moderate weight loss (5%) improves glycemic control and CVD risk factors
- all diabetics should see a registered dietician for nutrition counselling
- decrease combined saturated fats and trans fatty acids to <10% of calories
- avoid simple sugars, choose low glycemic index foods, ensure regularity in timing and spacing of meals

• physical activity and exercise
- at least 150 min of aerobic exercise plus 2 sessions of resistance training per wk is recommended
- encourage 30-45 min of moderate exercise 4-7 d/wk
- promote cardiovascular fitness: increases insulin sensitivity, lowers BP, and improves lipid profile
- if using insulin, may require alterations of diet, insulin regimen, injection sites, and self-monitoring

Self-Monitoring of Blood Glucose

• T1DM: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
• T2DM: recommendations vary based on treatment regimen (e.g. insulin dependent requires more frequent monitoring – refer to 2020 Diabetes Canada Clinical Practice Guidelines)
• if FBG >14 mmol/L, perform ketone testing to rule out DKA
• if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia

Remission of T2DM

• defined as achieving prediabetes or normal HbA1C levels without any antihyperglycemic medications for a minimum of 3 mo
• may be considered for individuals with:
- early T2DM who are overweight or obese

SMART
Diabetes Quick Reference Guide

A A1C: Optimal Glycemic Control (Usually <7%)
B BP: Optimal Blood Pressure Control (≤130/80)
C Cholesterol: LDL-C <2 mmol/L if treating
D Drugs: Consider ACEI/ARB, Statin, and ASA
E Exercise/Eating
S Smoking Cessation

Calculate Total Insulin Required
T1DM: 0.5-0.7 units/kg/d
T2DM: 0.3 units/kg/d
More information on insulin prescription, available at:
1) https://guidelines.diabetes.ca/CDACPG/media/documents/hcp-resources/Insulin_Prescription_Fillable_EN_02_21.pdf
2) https://guidelines.diabetes.ca/docs/resources/in-hospital-management-clinical-order-set-fillable.pdf

Rosiglitazone Revisited: An Updated VertiMeta-Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality
Arch Intern Med 2010;170:1191-1201
Purpose: To evaluate the effectiveness of rosiglitazone on MIs and mortality.
Methods: Systematic review of RCTs of rosiglitazone, lasting at least 24 wk in duration, and reporting CV adverse events. Main outcomes were MIs, CV-related mortality, and all-cause mortality.
Results: Rosiglitazone significantly increased MI risk (OR 1.28, 95% CI 1.02-1.63, P=0.04) but not CV mortality (OR 1.03, 0.78-1.36, P=0.86).
Conclusion: Rosiglitazone continues to demonstrate increased risk of MIs, though it is not associated with increased risk of CV or all-cause mortality.

Differential Diagnosis of Vertigo

	BPPV	Labyrinthitis	Menière's	Acoustic Neuroma
Onset	Sudden	Sudden	Gradual	Insidious
Duration	Seconds	Days	Min-h	Chronic
Hearing Loss	–	+	+	+
Tinnitus	–	+	+	+
Neuro Symptoms	–	–	–	+

- motivation and ability to pursue weight loss to de-escalate and/or eliminate use of antihyperglycemic agents
- no significant eating or mental health disorders, atherosclerotic CVD, CHF and/or CKD

• sustained weight loss of ≥15 kg of initial body weight is associated with the greatest probability of T2DM remission

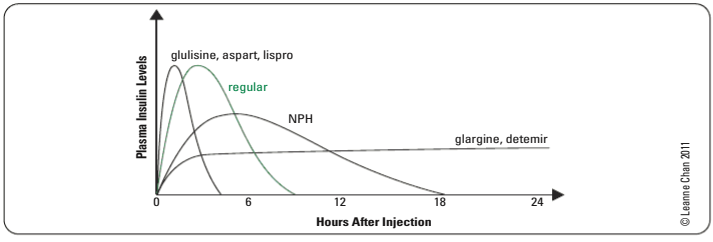
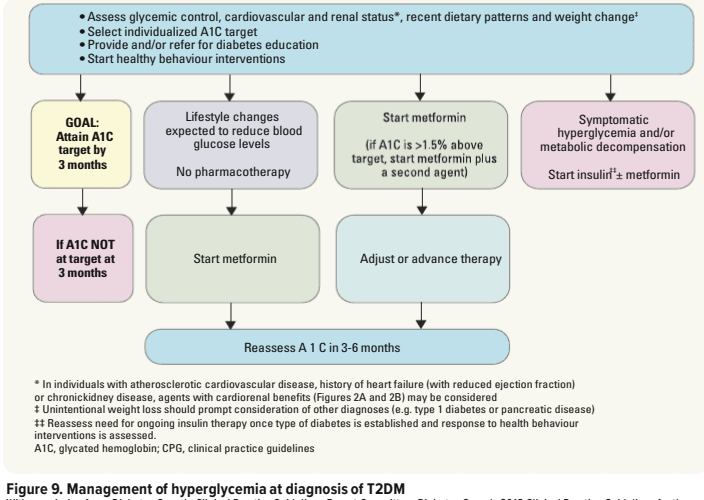


Figure 8. Types of insulin preparation


• Assess glycemic control, cardiovascular and renal status*, recent dietary patterns and weight change‡
• Select individualized A1C target
• Provide and/or refer for diabetes education
• Start healthy behaviour interventions
GOAL: Attain A1C target by 3 months
Lifestyle changes expected to reduce blood glucose levels
No pharmacotherapy
Start metformin
(if A1C is >1.5% above target, start metformin plus a second agent)
Symptomatic hyperglycemia and/or metabolic decompensation
Start insulin‡‡± metformin
If A1C NOT at target at 3 months
Start metformin
Adjust or advance therapy
Reassess A 1 C in 3-6 months

* In individuals with atherosclerotic cardiovascular disease, history of heart failure (with reduced ejection fraction) or chronickidney disease, agents with cardiorenal benefits (Figures 2A and 2B) may be considered
‡ Unintentional weight loss should prompt consideration of other diagnoses (e.g. type 1 diabetes or pancreatic disease)
‡‡ Reassess need for ongoing insulin therapy once type of diabetes is established and response to health behaviour interventions is assessed.
A1C, glycated hemoglobin; CPG, clinical practice guidelines

Figure 9. Management of hyperglycemia at diagnosis of T2DM
With permission from: Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2018;42(Suppl 1):S1-S325.

Pharmacologic Agents (T2DM)

• oral
- biguanides: metformin (Glucophage®)
- thiazolidinediones: pioglitazone (Actos®), rosiglitazone (Avandia®)
- α-glucosidase inhibitors: acarbose (Precose®)
- non-sulfonylurea insulin secretagogues: repaglinide (Gluconorm®)
- sulfonylureas: glyburide (DiaBeta®), glimepiride (Amaryl®), gliclazide (Diamicron®)
- DPP-4 inhibitors: sitagliptin (Januvia®), linagliptin (Trajenta®)
- SGLT2 inhibitors: canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®)

• injectable
- GLP-1 analogues: liraglutide (Victoza®), semaglutide (Ozempic®)

Other Medications Used in DM

• ACEI or ARB in those with any of:
- clinical macrovascular disease
- age ≥55
- age <55 and microvascular complications

• statin in those with any of:
- clinical macrovascular disease
- age ≥40
- age <40 and any of the following:
  - diabetes duration >15 yr and ages >30 yr
  - microvascular complications
  - other cardiovascular risk factors

• low dose ASA (81-325 mg)
- for secondary prevention in people with established CVD (NOT to be used routinely for primary prevention)

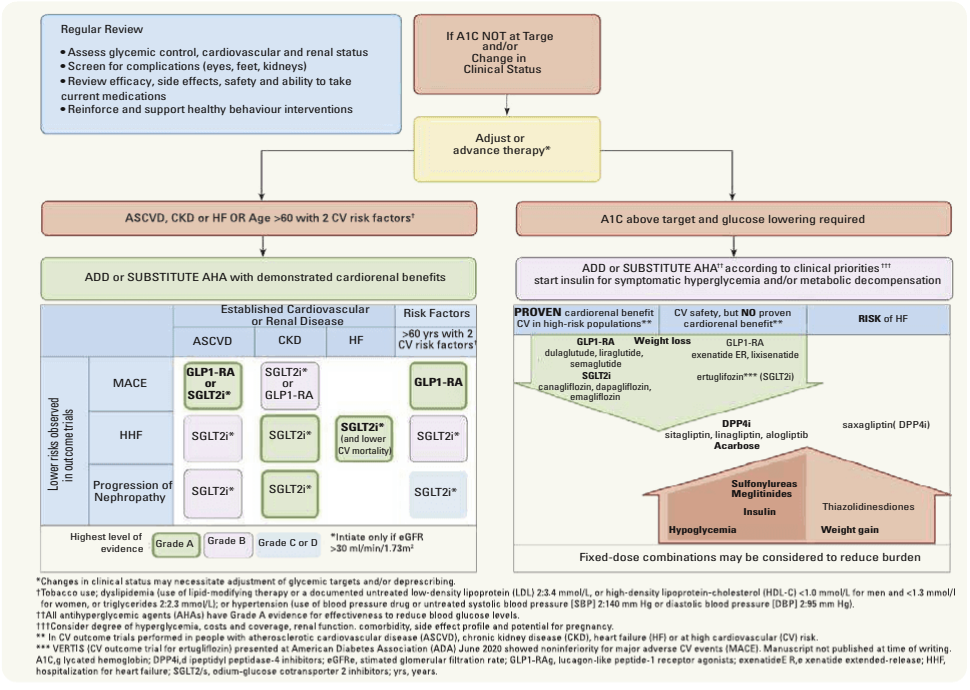

Regular Review
• Assess glycemic control, cardiovascular and renal status
• Screen for complications (eyes, feet, kidneys)
• Review efficacy, side effects, safety and ability to take current medications
• Reinforce and support healthy behaviour interventions
If A1C NOT at Targe and/or Change in Clinical Status
Adjust or advance therapy*
ASCVD, CKD or HF OR Age >60 with 2 CV risk factors†
A1C above target and glucose lowering required
ADD or SUBSTITUTE AHA with demonstrated cardiorenal benefits
ADD or SUBSTITUTE AHA†† according to clinical priorities ††† start insulin for symptomatic hyperglycemia and/or metabolic decompensation
Established Cardiovascular or Renal Disease
Risk Factors
ASCVD
CKD
HF
>60 yrs with 2 CV risk factors†
Lower risks observed in outcome trials
MACE
HHF
Progression of Nephropathy
GLP1-RA or SGLT2i*
SGLT2i* or GLP1-RA
SGLT2i*
SGLT2i* (and lower CV mortality)
GLP1-RA
SGLT2i*
Highest level of evidence
Grade A
Grade B
Grade C or D
*Intiate only if eGFR >30 ml/min/1.73m²
PROVEN cardiorenal benefit CV in high-risk populations**
CV safety, but NO proven cardiorenal benefit**
RISK of HF
GLP1-RA
dulaglutide, liraglutide, semaglutide
Weight loss
GLP1-RA
exenatide ER, lixisenatide
SGLT2i
canagliflozin, dapagliflozin, emagliflozin
ertuglifozin*** (SGLT2i)
DPP4i
sitagliptin, linagliptin, alogliptib
saxagliptin(DPP4i)
Acarbose
Sulfonylureas
Meglitinides
Insulin
Thiazolidinesdiones
Hypoglycemia
Weight gain
Fixed-dose combinations may be considered to reduce burden
*Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing.
†Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) 2:3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/l for women, or triglycerides 2:2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure (SBP) 2:140 mm Hg or diastolic blood pressure (DBP) 2:95 mm Hg).
††All antihyperglycemic agents (AHAs) have Grade A evidence for effectiveness to reduce blood glucose levels.
†††Consider degree of hyperglycemia, costs and coverage, renal function. comorbidity, side effect profile and potential for pregnancy.
** In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk.
*** VERTIS (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing.
A1C,g lycated hemoglobin; DPP4i,d ipeptidyl peptidase-4 inhibitors; eGFRe, stimated glomerular filtration rate; GLP1-RAg, lucagon-like peptide-1 receptor agonists; exenatideE R,e xenatide extended-release; HHF, hospitalization for heart failure; SGLT2i/s, odium-glucose cotransporter 2 inhibitors; yrs, years.

Figure 10. Reviewing, adjusting, or advancing therapy in T2DM
Reproduced with permission from Diabetes Canada. Diabetes Canada Clinical Practice Guidelines Expert Committee. Pharmacologic glycemic management of type 2 diabetes in adults: 2020 update. Can J Diabetes. 2020 Oct 1;44(7):575-91.

Dizziness

• see Otolaryngology, OT6

Epidemiology

• 70% of affected patients see general practitioners initially, 4% are referred to specialists
• frequency is proportional to age; commonest concern of ambulatory patients age >75

Differential Diagnosis

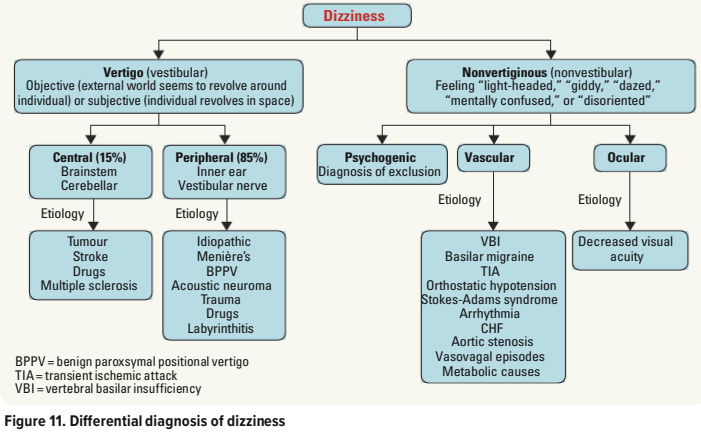


Figure 11. Differential diagnosis of dizziness

History
- clarify type of dizziness: vertigo, pre-syncope, disequilibrium, lightheadedness
- duration
- exacerbations
  - worse with head movement or eye closure (vestibular)
  - no change with head movement and eye closure (non-vestibular)
  - worse with exercise (cardiac/pulmonary causes)
- associated symptoms
  - neurologic (central)
    - transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
    - persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)
  - audiologic (peripheral)
    - hearing loss, tinnitus, otalgia, aural fullness
  - others
    - N/V (peripheral vestibular disorders)
    - breathlessness, palpitations (hyperventilation, cardiac problem)
- general medical history
  - HTN, DM, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
  - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - hypotension (secondary to diuresis): furosemide, caffeine, alcohol
  - depression/anxiety: can present with light-headedness

Physical Exam/Investigations
- syncopal
  - cardiac (orthostatic changes in vitals), peripheral vascular, and neurologic exams
  - blood work, ECG, 24 h Holter, treadmill stress test, loop ECG, tilt table testing, carotid and/or vertebral doppler, and EEG
- vertiginous
  - ENT and neurologic exams (head impulse, nystagmus, test of skew, HINTS exam)
  - Dix-Hallpike, consider audiometry, and MRI if indicated
- non-syncopal, non-vertiginous
  - assess gait, vision, and test for neuropathy
  - cardiac and neurologic exams (cerebellar and cranial nerve function)
  - 3 min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG
  - Romberg test: test for disequilibrium due to impaired proprioception

Treatment
- guided by history, physical exam, and investigations
- include education, lifestyle modification, physical maneuvers (e.g. Epley or Dr. Carol Foster's technique for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy, and surgery
- refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or if atypical presentation

Dix-Hallpike Test

Have the patient seated with legs extended and head at 45° rotation

Rapidly shift patient to supine position with head fully supported in slight extension (for 45 s)

Observe for rotatory nystagmus and ask about sensation of vertigo

Domestic Violence/Elder Abuse/Child Abuse

INTIMATE PARTNER VIOLENCE

Definition
- includes physical, sexual, emotional, psychological, and financial abuse

Epidemiology
- lifetime prevalence of intimate partner violence against women is between 25-30%
- similar prevalence of intimate partner violence against men, who may be less likely to report due to social stigma
- women who experience abuse have increased rates of injury, death, and health consequences including 50-70% increase in gynecological, central nervous system, and stress-related problems
- remember that men can also be victims of abuse
- occurs in all socioeconomic, educational, and cultural groups with increased incidence in pregnancy, disabled women, transgender and non-binary individuals, bisexuality, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where partner abuse occurs; children exposed to violence in the home are more likely to experience or perpetrate violence later in life (Cycle of Violence)
- physician recognition rates as low as 5%

Presentation
- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

Management
- maintain a high index of suspicion
  - asking about abuse is the strongest predictor of disclosure

Screening Instruments for Domestic Violence

Note: It is important to be mindful that the clinical relevance of the following screening tools may vary. Additionally, should they be relevant, one must take care to reduce distress and maintain patients' trust during these difficult conversations. Helpful strategies include interviewing the patient alone in a safe environment. Consider starting the discussion with "It is important to ask about people's close relationships", or "Do you feel safe in your current relationships?" While domestic violence may seem likely, the patient may not report it during the first encounter. Remember to screen for comorbid depression, anxiety, and substance misuse in suspected victims of domestic violence.

A) Woman Abuse Screening Tool (WAST)-SHORT

1. In general how would you describe your relationship?
   a. A lot of tension
   b. Some tension
   c. No tension
2. Do you and your partner work out arguments with . . .?
   a. Great difficulty
   b. Some difficulty
   c. No difficulty

Endorsing either question 1 ("a lot of tension") or question 2 ("great difficulty") makes intimate partner violence exposure likely

B) HITS

How often does your partner:
1. Physically hurt you?
2. Insult you?
3. Threaten you with harm?
4. Scream or curse at you?

Each question on HITS to be answered on a 5 point scale ranging from 1 (= never) to 5 (= frequently)
A total score of 10 or greater is significant

  - consider asking if patient feels safe at home or in their relationships; several screening tools (see sidebar) exist to identify victims of intimate partner violence
  - make sure to determine the victim's level of immediate and long-term danger and ask if there are weapons in the house
- ensure patient safety
  - victim most at risk for homicide when attempting to leave home or following separation
  - safety planning includes ensuring that there is access to an exit in the home, establishing a safe place to go, and having emergency items prepared should the patient need to leave quickly (including money, clothes, keys, medications, and important documents)
- provide community resources
  - shelter or helpline number with legal advocacy and counselling services
  - involve social workers or domestic violence advocates with the patient's consent
- appointment for follow-up to assess whether condition is better or worse
- reassure patient is not to blame and that the assault is a crime
- goal is to convey support
  - reporting suspected or known child abuse is mandatory
  - spousal abuse is a criminal act, but not reportable without the person's permission
- DOCUMENT all evidence of abuse-related visits for medico-legal purposes; aim to provide verbatim quotations, when possible

ELDER ABUSE
- see Geriatric Medicine, GM7

CHILD ABUSE
- see Pediatrics, P18

Dyspepsia

- see Gastroenterology, G10

Definition and Clinical Features
- defined as epigastric pain or discomfort
- can be associated with fullness, belching, bloating, heartburn, food intolerance, N/V

Epidemiology
- annual incidence 1-2%, prevalence 20-40%

Etiology
- common: functional, PUD, GERD, gastritis
- others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

History
- symptoms may not be useful in finding cause
- associated with eating, anorexia, N/V, alcohol, NSAID use
- red flags: vomiting, bleeding/anemia, abdominal mass, dysphagia (VBAD)

Investigations
- for new onset dyspepsia:
  - <60 yr without high-risk features, test for *H. pylori* using the urea breath test, stool antigen test, or serology
  - ≥60 yr should undergo upper endoscopy to rule out organic pathology

Management
- lifestyle modifications: decrease caffeine and alcohol intake, avoid citrus food, smaller and more frequent meals, avoid supine position right after meals, smoking cessation
- pharmacologic treatment
  - gastric acid suppression: H2 blockers, PPIs; both are effective for PUD and GERD
  - TCAs or prokinetics: e.g. metoclopramide; effective for functional dyspepsia
- *H. pylori* eradication
  - do not keep patients on PPI without at least 1 trial off the medication per year (https://choosingwiselycanada.org/perspective/ppi-toolkit/)
- for non-responders, upper endoscopy should be considered. If endoscopy is negative, defined as functional dyspepsia

Dyspepsia Red Flags
Weight loss
Dysphagia
Persistent vomiting
GI bleeding (hematemesis, hematochezia, melena)
Onset age >50

***H. pylori* Eradication**
Bismuth Quadruple Therapy (PBMT) or Concomitant Non-Bismuth Quadruple Therapy (PAMC) for 14 days

PBMT:
1) PPI standard dose BID
2) Bismuth subsalicylate 524 mg QID
3) Metronidazole 500 mg QID
4) Tetracycline 500 mg QID

PAMC:
1) PPI standard dose BID
2) Clarithromycin 500 mg BID
3) Amoxicillin 1000 mg BID
4) Metronidazole 500 mg BID

Dyspnea

• see Respirology, R3 and Emergency Medicine, ER26

Definition
- uncomfortable, abnormal awareness of breathing, a subjective sensation of shortness of breath, or difficulty breathing
- when discussing dyspnea with patients, consider using language that is easy for patients to understand such as speaking about "feeling breathless" or "having trouble catching your breath"

History and Physical Exam
- history
  - associated symptoms (cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema)
  - constitutional symptoms (night sweats, fever, weight loss)
  - history of asthma, allergies, eczema, ASA/NSAID sensitivity, nasal polyps
  - smoking, recreational drugs, medications
  - occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  - travel and birthplace (considering areas with increased prevalence of TB)
  - family history of atopy
  - previous CXR or PFTs
- physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

Investigations
- CXR, ECG
- PFTs, ABG acutely if indicated

Management
- dependent on cause
- send to ED if acute presentation with moderate symptoms
- call ambulance if in severe respiratory distress

Differential Diagnosis of Dyspnea

Pulmonary
- COPD
- Asthma
- Restrictive lung disease
- Pneumothorax
- Congenital lung disease
- PE
- Malignancy

Cardiac
- HF
- CAD
- MI (recent or past)
- Cardiomyopathy
- Valvular dysfunction
- Pericarditis
- Arrhythmia
- Hypertrophy

Mixed/Other
- Deconditioning
- Psychological and/or physical trauma
- Pain
- Neuromuscular
- Metabolic condition
- Anemia
- Functional: anxiety, panic attack, hyperventilation

Dysuria

• see Urology, U10

Definition
- the sensation of pain, burning, or discomfort when urinating

Epidemiology
- more common in women than men
- approximately 25% of women report one episode of acute dysuria per yr
- most common in women ages 25-54 and in those who are sexually active
- in men, prevalence of dysuria increases with age

Etiology
- infectious
  - most common cause
  - presents as cystitis, urethritis, pyelonephritis, vaginitis, cervicitis, epididymo-orchitis, or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, radiation, drugs/chemicals, foreign bodies, trauma, neoplasm, kidney stones, inflammatory diseases, endometriosis, psychogenic

Table 13. Etiology, Signs, and Symptoms of Common Causes of Dysuria

Infection	Etiology	Signs and Symptoms
UTI/Cystitis	KEEPS bacteria (*Klebsiella, E. coli, Enterobacter* spp., *P. mirabilis, Pseudomonas* spp., *S. saprophyticus*)	Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)
Urethritis	*C. trachomatis, N. gonorrhoeae, Trichomonas* spp., *Candida* spp., herpes	Initial dysuria, urethral/vaginal discharge, history of STI
Vaginitis	*Candida* spp., *Gardnerella* spp., *Trichomonas* spp., *C. trachomatis*, atrophic, herpes, lichen sclerosis	External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding
Prostatitis	*E. coli, C. trachomatis, S. saprophyticus, P. mirabilis, Enterobacter* spp., *Klebsiella* spp., *Pseudomonas* spp.	Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain
Pyelonephritis	E. *coli, S. saprophyticus, P. mirabilis, Enterobacter* spp., *Klebsiella* spp., *Pseudomonas* spp.	Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, N/V

Investigations
- if history, physical, and urine dipstick are consistent with an uncomplicated UTI, treat empirically with no further investigations
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteriuria, hematuria

UTI Clinical Decision Aid

Arch Intern Med 2007;67:2201-2206
- Dysuria
- +Leukocytes (on urine dipstick)
- +Nitrites (on urine dipstick)

If 2 or more criteria met, then treat without culture, otherwise culture required prior to treatment.

Risk Factors for Complicated UTI
- Male
- Pregnancy
- Recent urinary tract instrumentation
- Functional or anatomic abnormality of the urinary tract
- Chronic renal disease
- DM
- Immunosuppression
- Indwelling catheter

Cranberries for Preventing Urinary Tract Infections

Cochrane DB Syst Rev 2023;10:CD001321

Purpose: To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations.

Methods: All RCTs or quasi-RCTs of cranberry products for the prevention of UTIs were assessed and a meta-analysis of 50 RCTs (n=8857) conducted.

Results: Cranberry products reduced the incidence of symptomatic, culture-verified UTIs in women with recurrent UTIs (RR 0.74; 95% CI, 0.55-0.99), in children (RR 0.46; 95% CI, 0.32-0.68), and in people with intervention-related UTI susceptibility (RR 0.47; 95% CI, 0.37-0.61) compared with controls.

Conclusion: Cranberry products reduce the risk of symptomatic UTIs in certain populations.

- urine C&S
- CBC and differential if suspecting pyelonephritis
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomonas, endocervical/urethral swab or urine PCR for N. gonorrhoeae and C. trachomatis
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P69 for UTI

Management

- hospitalize if septic or critically ill, and consider hospitalization if persistently high fever, persistent pain, severe weakness, or inability to maintain hydration or tolerate oral feeds
- first-line treatment of uncomplicated UTI is TMP/SMX (cotrimoxazole) 160/800 mg BID x 3 d or nitrofurantoin 100 mg BID x 5 d
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated (first line: amoxicillin, nitrofurantoin (avoid in third trimester), cephalexin) even if asymptomatic due to increased risk of pyelonephritis, preterm labour, low birth weight, and perinatal mortality. Need to follow with monthly urine cultures and repeat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
- urethritis
  - positive swab or PCR for chlamydia or gonorrhea must be reported to Public Health (see Family Medicine, FM47for management of STIs)
  - all patients should return 4-7 d after completion of therapy for clinical evaluation

Prevention of UTIs
- Maintain good hydration
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse
- Vaginal estrogen therapy for peri- and postmenopausal women with recurrent UTIs

Epistaxis

- see Otolaryngology, OT27

Erectile Dysfunction

- see Urology, U33

Definition

- >3 mo of consistent or recurrent inability to attain and/or maintain sufficient penile erection for sexual performance

Epidemiology

- ~20% of men age 40; ~50% of men age 70

Etiology

- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, DM), anatomic (structural abnormality, e.g. Peyronie's), neurologic (postoperative, DM), medications (clonidine, antihypertensives, SSRIs, tricyclic antidepressants, cimetidine, 5-α-reductase inhibitors)
- psychogenic (10%)

Differential Diagnosis of Erectile Dysfunction

PENIS
Psychogenic
Endocrine (T2DM, testosterone)
Neurogenic (T2DM, postoperative)
Insufficiency of blood (atherosclerosis)
Substances

Table 14. Differentiation Between Organic and Psychogenic ED

Characteristic	Organic	Psychogenic
Onset	Gradual	Acute
Circumstances	Global	Situational
Course	Constant	Varying
Non-Coital Erection	Poor	Rigid
Morning Erection	Absent	Present
Psychosexual Problem	Secondary	Long history
Partner Problem	Secondary	At onset
Anxiety and Fear	Secondary	Primary

Walsh PC, Campbell MF, Retik AB. Campbell's Urology, 8th ed. W.B. Saunders, 2002. Table 46-4

History

- comprehensive sexual, medical, and psychosocial history
  - review medication and substance use
- time course
  - last satisfactory erection
  - gradual or sudden onset
  - attempts at sexual activity
- quantify
  - presence of morning or night time erections
  - stiffness (scale of 1-10)
  - ability to initiate and maintain an erection with sexual stimulation
  - erection stiffness during sex (scale of 1-10)

- qualify
  - partner or situation specific
  - loss of erection before penetration or climax
  - degree of concentration required to maintain an erection
  - percentage of sexual attempts satisfactory to patient and/or their partner
  - significant bends in penis or pain with erection
  - difficulty with specific positions
  - impact on quality of life and relationship

Investigations
- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: FBG, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
  - psychological and/or psychiatric consultation
  - in-depth psychosexual and relationship evaluation
  - nocturnal penile tumescence and rigidity (NPTR) assessment
  - vascular diagnostics (e.g. doppler studies, angiography)

Management

Table 15. Management of Erectile Dysfunction

Nonpharmacologic	Pharmacologic	Surgical
Lifestyle changes (alcohol, smoking, exercise) Relationship/sexual counselling Vacuum devices	Oral agents Suppository Male urethral suppository for erection (MUSE) Injections	Implants Vascular repair Realignment

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors
  - testosterone (currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications))
  - α-adrenergic blockers (e.g. yohimbine); currently limited data for use in erectile dysfunction

Table 16. Phosphodiesterase Type 5 Inhibitors

Examples	Dosing (1 dose/d)	Specifics	Side Effects	Contraindications
sildenafil (Viagra®)	25-100 mg/dose	Take 0.5-4 h prior to intercourse May last 24 h	Flushing, headache, indigestion	Not to be used in patients taking nitrates
tadalafil (Cialis®)	5-20 mg/dose	Effects may last 36 h	As above	As above
vardenafil (Levitra®)	2.5-20 mg/dose	Take 1 h prior to intercourse	As above	As above

The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction
Arch Intern Med 2011;171:1797-1803
Purpose: To evaluate the effectiveness of lifestyle interventions and pharmacotherapy for cardiovascular (CV) risk factors on severity of erectile dysfunction (ED).
Methods: Meta-analysis of RCTs with a follow-up of a minimum of 6 wk, evaluating lifestyle intervention vs. pharmacotherapy for CV risk factor reduction. Main outcome measure was weighted mean differences in the International Index of Erectile Dysfunction (IIEF-5) score.
Results: 6 RCTs with a total of 740 participants were included. Lifestyle modifications and pharmacotherapy for CV risk factor reduction were both associated with significant improvements in sexual function based on IIEF-5 scores (weighted mean difference (WMD) 2.66, 95% CI 1.86-3.47). Excluding statin trials, lifestyle modification interventions were associated with a statistically significant improvement in sexual function (WMD 2.40, 1.19-3.61).
Conclusion: Lifestyle modifications and pharmacotherapy for CV risk reduction are effective in improving male sexual function.

Reasons for Referral to Urology
- Significant penile anatomic disease
- Younger patient with a history of pelvic or perineal trauma
- Cases requiring vascular or neurosurgical intervention
- Complicated endocrinopathies
- Complicated psychiatric or psychosocial problems
- Patient or physician desire for further evaluation

Fatigue

Definition
- can describe difficulty or inability to initiate activity, maintain activity, or difficulty with concentration/memory
- presentation may vary and the patient's specific complaint should be clarified, e.g. excessive sleepiness, muscle weakness, decreased exercise tolerance, mood concerns

Epidemiology
- 25% of office visits to family physicians
  - peaks in ages 20-40
  - F:M=3-4:1
- 50% have associated psychological complaints/problems, especially if <6 mo duration

Differential Diagnosis

Table 17. Differential Diagnosis of Fatigue: PS VINDICATE

P	**Psychogenic**	**Depression, life stresses**, anxiety disorder, chronic fatigue syndrome, fibromyalgia
	Physiologic	Pregnancy, caregiving demands (young children, elderly)
S	Sleep disturbance	**OSA**, **sleep disorder**, poor sleep hygiene, BPH, shift work, pain
	Sedentary	Unhealthy/sedentary lifestyle
V	**Vascular**	Stroke
I	**Infectious**	Viral (e.g. mononucleosis, hepatitis, HIV), bacterial (e.g. TB), fungal, parasitic
N	Neoplastic	Any malignancy
	Nutrition	**Anemia** (Fe^{2}deficiency, B 12deficiency)
	Neurogenic	Myasthenia gravis, multiple sclerosis, Parkinson's disease
D	**Drugs**	β-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics, antidepressants
I	Idiopathic	
C	Chronic illnesses	HF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease
A	Autoimmune	SLE, RA, mixed connective tissue disease, polymyalgia rheumatica
T	Toxin	**Substance misuse** (e.g. alcohol), heavy metal
E	Endocrine	**Hypothyroidism, DM** , Cushing's syndrome, adrenal insufficiency, pregnancy

Common causes are in **bold**

Investigations

- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical exam
- investigations are guided by history and physical exam and may include:
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vitamin B12, serum protein electrophoresis, Bence-Jones protein, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - urinalysis, CXR, ECG
  - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests

Treatment

- treat underlying cause
- if etiology cannot be identified (1/3 of patients)
  - validation and follow-up, especially with fatigue of psychogenic etiology
  - supportive counselling, behavioural, or group therapy
  - encourage patient to stay physically active to maximize function, and consider using motivational interviewing techniques to create person-centred approaches
  - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
  - prognosis: after 1 yr, 40% are no longer fatigued

CHRONIC FATIGUE SYNDROME

Diagnosis (Institute of Medicine, 2015)

- diagnosis requires the following three symptoms:
  1. a substantial reduction or impairment in the ability to engage in pre-illness levels of activity that is:
     - lasting >6 mo
     - accompanied by fatigue of new onset, not alleviated by rest, and not caused by excessive exertion
  2. post-exertional malaise*
     - worsening of symptoms after physical, mental or emotional exertion that would not have caused a problem before the illness
  3. unrefreshing sleep*
     - even after a full night of sleep despite the absence of specific objective sleep alterations

  AND
  - at least one of the two following manifestations is also required:
    - cognitive impairment*
    - orthostatic intolerance

*The frequency and severity of these symptoms need to be evaluated

Epidemiology

- F>M, more common in White individuals than other groups, majority in their 30s
- found in <5% of patients presenting with fatigue

Etiology

- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency

Exercise Therapy for Chronic Fatigue
Cochrane DB Syst Rev 2019;10:CD003200
Purpose: To determine the effects of exercise therapy for adults with chronic fatigue syndrome (CFS) compared with any other intervention or control.
Methods: Meta-analysis of RCTs involving adults with CFS as a primary diagnosis who were able to participate in exercise therapy. Studies compared exercise therapy to passive control, psychological therapies, adaptive pacing therapy, or pharmacological therapy.
Results: Eight RCTs with 1518 participants were included. Exercise therapy lasted 12 to 26 wk. Moderate quality evidence showed exercise therapy was more effective in reducing fatigue vs. passive or no treatment, and was also associated with a positive effect on daily physical functioning and sleep. It also slightly improved physical functioning, depression, and sleep compared to adaptive pacing.
Conclusion: Exercise therapy may have a positive effect on fatigue in adults with CFS compared to usual care or passive therapies.

Investigations
- no specific diagnostic laboratory tests

Treatment
- promote sleep hygiene
- provide support and education that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy, family therapy, support groups
  - consider using motivational interviewing techniques to create person-centred approaches
- pharmacological
  - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials (if indicated based on investigations), anti-allergy therapy, antihypotensive therapy

Fever

- see Pediatrics, P58

Definition
- oral temperature >37.2°C (AM), >37.7°C (PM), rectal temperature 37.5°C–38.3°C, or axillary temperature >37.2°C
- fever in children <2 yr must be a rectal temperature for accuracy
- TM not accurate for measurement until child is >5 yr

Table 18. Differential Diagnosis of Fever

Infection	Cancer	Medications		Other
Bacterial	Leukemia	Allopurinol	Nifedipine	Inflammatory Bowel Disease
Viral	Lymphoma	Captopril	Phenytoin	Collagen Vascular Disease
TB	Other Malignancies	Cimetidine	Diuretics	DVT
		Heparin	Barbiturates	
		INH	Antihistamines	
		Meperidine		

History
- fever
  - peak temperature, type of thermometer, site of temperature measurement, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
- symptoms of possible source
  - URTI: cough, coryza, ear pain (consider influenza, COVID-19)
  - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
  - pneumonia: cough, pleuritic chest pain
  - meningitis: headache, confusion, stiff neck, rash
  - osteomyelitis: bone pain
  - skin: purulent discharge
  - PID: discharge, dyspareunia, lower abdominal pain
  - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
  - medications
  - PE/DVT: swollen legs, pain in calf, SOB, pleuritic chest pain
  - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, daycare, contact with TB, foodborne, animals

Possible Investigations
- CBC and differential, blood culture, urine culture, urinalysis
  - viral swab including influenza, COVID-19
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- lumbar puncture

Management
- increase fluid intake
- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause

Headache

Definitions
- primary headaches
- see Neurology, N46
  - primary headaches are the most common headaches seen in family medicine including tension headaches, migraines, and cluster headaches
  - secondary causes should be ruled out prior to diagnosing a patient with a primary headache
- secondary headaches
  - caused by underlying organic disease
  - account for <10% of all headaches, may be life-threatening

Etiology of Secondary Headaches
- drug: drug withdrawal, medication overuse, drug side effect, and carbon monoxide
- infectious: meningitis, encephalitis, abscess
- vascular: aneurysm, stroke, SAH, HTN, and temporal arteritis
- endocrine: thyroid disease, pheochromocytoma
- neoplastic: tumour
- trauma: TMJ injury, c-spine injury, head injury, subdural hematoma, and SAH
- other: serious ophthalmological and otolaryngological causes

Investigations
- indicated only when red flags are present and may include:
  - CBC for suspected systemic or intracranial infection
  - ESR or CRP for suspected temporal arteritis
  - neuroimaging (CT or MRI) to rule out intracranial pathology
  - CSF analysis for suspected intracranial hemorrhage, infection

Management
- based on underlying disorder
- analgesics may provide symptomatic relief
  - see Neurology, N47

Hearing Impairment

- see Otolaryngology, OT9

Definition
- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

Classification
- conductive (external sound does not reach the inner ear)
- sensorineural (involving the inner ear, cochlea, or auditory nerve)
- mixed

Epidemiology
- prevalence increases with age (6% of 35-44 yr, 43% of 65-84 yr)
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people >65 yr

Assessment
- infants: universal newborn hearing screening program
- elderly
- screening tests
  - whispered-voice test
    - examiner stands 0.6 metres (arm's length) behind the patient, whispers a combination of 6 letters/numbers, and asks the patient to repeat the sequence. Test 1 ear at a time while masking the non-test ear simultaneously
  - Rinne and Weber tuning fork tests (to distinguish conductive from sensorineural hearing loss)
- diagnostic tests (formal audiologic assessment)
  - pure tone, air, and bone conduction testing
  - speech audiometry
  - impedance audiometry

Acupuncture for Migraine Prophylaxis
Cochrane DB Syst Rev 2016:6:CD001218
Purpose: To investigate whether acupuncture is more effective than routine care (no prophylaxis), sham acupuncture, or prophylactic pharmacological treatment at reducing episodic migraine frequency in adults.
Methods: Meta-analysis of 22 RCTs (n=4985) with a minimum of an 8 wk duration, comparing acupuncture intervention with a non-acupuncture control (no prophylaxis, routine care, sham, or pharmacological prophylaxis.
Results: Acupuncture moderately reduced headache frequency compared to no acupuncture (standardized mean difference (SMD) -0.56,; 95% CI, -0.65 to -0.48)). Acupuncture showed a small but statistically significant reduction over sham post-treatment (SMD -0.18; 95% CI -0.28 to -0.08) and post-follow-up (SMD -0.19; 95% CI -0.30 to -0.09). Compared to pharmacological prophylaxis, a significant reduction in migraine frequency was noted with acupuncture treatment (SMD -0.25; 95% CI -0.39 to -0.10), but significance was not maintained at follow-up.
Conclusion: Adding acupuncture to symptomatic treatment of attacks reduces frequency of headaches. Acupuncture is more effective than sham, and is similarly effective to pharmacological interventions for migraine prophylaxis.

Migraine Screen

POUND
Pulsatile quality
Over 4-72 h
Unilateral
Nausea and vomiting
Disabling intensity
If ≥4 present then a diagnosis is likely (Positive likelihood ratio = 24)

Headache Red Flags

SNOOP
Systemic symptoms of illness
- Fever
- Anticoagulation
- Pregnancy
- Cancer

Neurologic signs/symptoms
- Impaired mental status
- Neck stiffness
- Seizures
- Focal neurological deficits

Onset
- Sudden and severe
- New headache after age 50

Other associated conditions
- Following head trauma
- Awakens patient from sleep
- Jaw claudication
- Scalp tenderness
- Worse with exercise, sexual activity, or Valsalva

Prior headache history
- Different pattern
- Rapidly progressing in severity/ frequency

Management
- counsel about noise control and hearing protection programs (high quality evidence)
  - treat patients with unexplained, unilateral, sudden sensorineural hearing loss urgently with steroids
  - consider blood glucose, CBC and differential, TSH, syphilis testing for unexplained sensorineural hearing loss
  - consider a CT/MRI for patients with progressive asymmetric sensorineural hearing loss to exclude vestibular schwannoma (acoustic neuroma)
- refer patients who
  - have an unknown etiology to an ENT specialist
  - experience sudden sensorineural hearing loss to an ENT specialist for ongoing care
- treatment: hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life

Hypertension

- Hypertension guidelines are reviewed and updated annually, for up-to-date recommendations, please see http://guidelines.hypertension.ca/

Definitions
- HTN
  - if diabetic, office BP measurement (OBPM) ≥130/80 mmHg for ≥3 measurements on different days = probable HTN, rule out white coat HTN
  - if not diabetic and automated office BP (AOBP) ≥135/85 mmHg or OBPM ≥140/90 mmHg, rule out white coat HTN
    - ambulatory BP monitoring (ABPM) daytime mean ≥135/85 mmHg OR ABPM 24 hr mean ≥130/80 mmHg = HTN
    - home BP monitoring (HBPM) series mean ≥135/85 mmHg = HTN
    - mean AOBP or OBPM sBP ≥180 mmHg or dBP ≥110 mmHg = HTN
- isolated systolic HTN
  - sBP ≥140 mmHg and dBP <90 mmHg
  - associated with progressive reduction in vascular compliance
  - usually begins in 5th decade
- hypertensive urgency
  - sBP >210 mmHg or dBP >120 mmHg with minimal or no target-organ damage
- hypertensive emergency
  - severe HTN (dBP >120 mmHg) + acute target-organ damage (acute heart failure, MI, aortic dissection, acute kidney injury, hypertensive encephalopathy, hypertensive retinopathy)
  - accelerated HTN
    - significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy, but without papilledema
  - malignant HTN
    - sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
- white coat HTN
  - high clinic BP with normal home BP and 24 h ambulatory BP, caused by anxiety in clinic
- masked HTN
  - normal clinic BP with high BP in home and/or ambulatory setting, often provoked by anxiety, job stress, exercise

- Symptoms of HTN are usually not present (this is why it is called the "silent killer")
- Patients may have an occipital headache upon awakening or organ-specific complaints if advanced disease

Renovascular HTN Suspected if Patient Presenting with 2 or more of:
- Sudden onset or worsening of HTN and ages >55 or <30
- Presence of abdominal bruit
- HTN resistant to 3 or more drugs
- Rise in Cr of 30% or more associated with use of an ACEI or ARB
- Other atherosclerotic vascular disease, particularly in patients who smoke or have dyslipidemia
- Recurrent pulmonary edema associated with hypertensive surges

Epidemiology
- 22% of Canadian adults suffer from HTN (prevalence is 52% in the 60-70 age group)
- lifetime risk of developing HTN is approximately 90%
- 64% of Canadians who have HTN are treated and controlled, while 17% are unaware that they have HTN
- 3rd leading risk factor associated with death
  - risk factor for CAD, HF, cerebrovascular disease, renal failure, PVD

Etiology
- essential HTN (90%, undetermined cause)
- secondary HTN (10%, known cause)

Predisposing Factors
- family history
- obesity (especially abdominal)
- alcohol consumption
- stress
- sedentary lifestyle
- smoking
- male

- age >30
- excessive salt intake/fatty diet
- Black ancestry
- dyslipidemia

Table 19. Causes of Secondary HTN

	Common Cause		
Renal	Renovascular HTN Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney		
Endocrine	1º hyperaldosteronism Pheochromocytoma Cushing's syndrome Hyperthyroidism/hyperparathyroidism Hypercalcemia of any cause		
Vascular	Coarctation of the aorta Renal artery stenosis		
Other	OSA		
Drug-Induced	Estrogens/OCP MAOIs Cocaine	Steroids Lithium Amphetamines	NSAIDs Decongestants Alcohol

Suspect Hyperaldosteronism when
HTN refractory to treatment with ≥3 drugs
Spontaneous hypokalemia
Profound diuretic-induced hypokalemia (<3.0 mmol/L)
Incidental adrenal adenomas

Hypertensive Emergencies
Malignant HTN
Cerebrovascular
- Hypertensive encephalopathy
- Stroke
- Intracerebral hemorrhage
- SAH

Cardiac
- Acute aortic dissection
- Acute refractory LV failure
- Myocardial infarction/ischemia
- Acute pulmonary edema

Renal failure

Investigations

- for all patients with HTN:
  - electrolytes, Cr, FBG and/or HbA1c, lipid profile, 12-lead ECG, urinalysis
  - self-measurement of BP at home is encouraged (recommended devices listed at www.hypertension.ca)
- for specific patient etiology:
  - DM or chronic kidney disease: urinary protein excretion
  - if suspected renovascular HTN: renal ultrasound, captopril renal scan (if GFR >60 mL/min), MRA/CTA (if normal renal function)
  - if suspected endocrine cause: plasma aldosterone, plasma renin (aldosterone-to-renin ratio)
    - measured from morning samples taken from patients in sitting position after resting 15 min
    - discontinue aldosterone antagonists, ARBs, β-blockers, and clonidine prior to testing
  - if suspected pheochromocytoma: 24 h urine for metanephrines and creatinine
  - if suspected LV dysfunction: echocardiogram
  - if clinically indicated or with refractory hypertension: sleep study

Diagnosis

- all Canadian adults should have BP assessed at all appropriate clinical visits, oscillometric preferred to manual

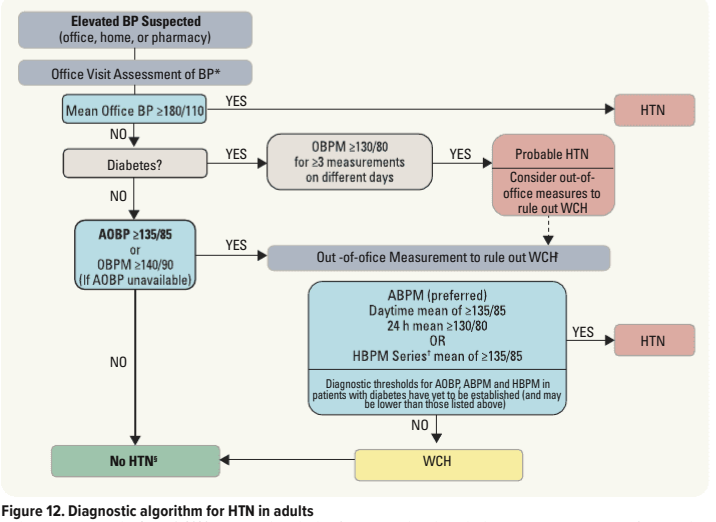


Figure 12. Diagnostic algorithm for HTN in adults
Rabi DM, et al. Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. Can J Cardiol. 2020;36(5):596–624. Reproduced with permission from Hypertension Canada.

Treatment

- hypertension means high pressure/strain. Without increasing a patient's potential distress, consider what may be causing their high pressure or strain. It may be important to support a patient in reducing sources of stress and worry
- treat to target BP: <140/90 mmHg, <130/80 mmHg if DM
- optimum management of HTN requires assessment of overall cardiac risk
- explore adherence to lifestyle modification and pharmacotherapy at each visit
- lifestyle modification (in all HTN patients – may be sufficient treatment in patients with stage 1 HTN (140-159/90-99 mmHg))
  - diet
    - follow Canada's Guide to Healthy Eating (see *Nutrition, FM7*) and DASH
    - limit daily salt intake to 5 g (2000 mg of sodium)
    - potassium/magnesium/calcium supplementations are NOT recommended for HTN, but an increase in dietary potassium may help
  - moderate intensity dynamic exercise: 30-60 min, 4-7x/wk; higher intensity exercise is not more effective
  - smoking cessation
  - low-risk alcohol consumption (see *Alcohol Use, FM15*)
  - work towards a healthy BMI (18.5-24.9 kg/m ^{2}) and waist circumference (<102 cm for men, <88 cm for women)
  - individualized approaches to reduce stress
- pharmacological
  - indications for antihypertensive therapy (caution with elderly patients):
    - sBP ≥140mmHg or dBP ≥90 mmHg with target organ damage or CV risk factors
    - sBP ≥160 mmHg or dBP ≥100 mmHg without target organ damage or CV risk factors
    - sBP ≥130 for high-risk populations (Framingham Risk >20%, ages >50)
    - sBP ≥130 mmHg or dBP ≥80 mmHg for patients with DM
  - first-line antihypertensives (consider a single pill combination therapy)
  - combination therapy principles:
    - if there is an inadequate response to therapy, consider adding another first line antihypertensive
    - avoid combining a non-DHP CCB with a β-blocker or an ACEI with an ARB
    - monitor potassium and creatinine when administering an ACEI/ARB with a potassium-sparing diuretic

Impact of Health Behaviour on Blood Pressure

Intervention	sBP (mmHg)	dBP (mmHg)
Diet and weight control	-6.0	-4.8
Reduced salt/ sodium intake	- 5.4	- 2.8
Reduced alcohol intake (heavy drinkers)	-3.4	-3.4
DASH diet	-11.4	-5.5
Physical activity	-3.1	-1.8
Relaxation therapies	-3.7	-3.5

CHEP (Canadian Hypertension Education Program) Guidelines 2014. Available from: https://www.onlinecjc.ca/article/S0828-282X(14)00070-1/fulltext

β-blocker
Not recommended as first line for patients of ages ≥60

ACEI
Not recommended as monotherapy in people of African descent

Table 20. Considerations in the Individualization of Pharmacological Therapy in Adults

Condition or Risk Factor	Recommended Drugs	Alternative Drugs	Not Recommended/Notes
Isolated Diastolic HTN with or without Systolic HTN	Monotherapy or single pill combination (SPC) Recommended monotherapy choices include thiazide/thiazide-like diuretics (with longer-acting diuretics preferred), β-blockers, ACEI, ARBs, or long-acting CCBs. Recommended SPC choices include combinations of an ACEI with CCB, ARB with CCB, or ACEI/ ARB with a diuretic. (Consider ASA and statins in selected patients)	Combinations of first-line drugs	Not recommended for monotherapy: α-blockers, β-blocker in those ≥60 yr, ACEI in Black people Hypokalemia should be avoided in those prescribed diuretics. ACEI, ARBs and direct renin inhibitors are potential teratogens, and caution is required if prescribing to women with childbearing potential. Combination of an ACEI with an ARB is not recommended
Isolated Systolic HTN without other compelling indications	Thiazide diuretic, ARB, or long acting DHP CCB	Combinations of first-line drugs	Same as above
CAD	ACEI or ARB; β-blockers or CCB for patients with stable angina	When combination therapy for high-risk patients, ACEI/DHP CCB is preferred	Avoid short-acting nifedipine. Combination of an ACEI with an ARB is specifically not recommended. Exercise caution when lowering sBP to target if dBP is ≤60 mmHg, especially in patients with LVH
Recent MI	β-blocker and ACEI (ARB if cannot tolerate ACEI)	Long-acting CCB if β-blocker contraindicated or not effective	Non-DHP CCBs should not be used with concomitant HF
Left Ventricular Hypertrophy	ACEI, ARB, thiazide/thiazide-like diuretics, or long-acting CCB	Combination of additional agents	Hydralazine and minoxidil can increase LVH, thus not recommended
Cerebrovascular Disease (stroke/TIA)	ACEI and thiazide/thiazide-like diuretic combination	Combination of additional agents	Treatment of HTN should not be routinely undertaken in acute stroke unless extreme BP elevation. ACEI and ARB combination after a stroke is not recommended

2020 Hypertension Highlights, Hypertension Canada.
https://hypertension.ca/wp-content/uploads/2018/07/Hypertension-Guidelines-English-2018-Web.pdf

Calcium Channel Blockers

Dihydropyridine CCBs
Amlodipine
Nifedipine
Felodipine
Non-dihydropyridine CCBs
Diltiazem
Verapamil

How to Combine Antihypertensive Medications (in general)

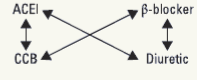


Table 20. Considerations in the Individualization of Pharmacological Therapy in Adults

Condition or Risk Factor	Recommended Drugs	Alternative Drugs	Not Recommended/Notes
Heart Failure	ACEI (ARB if ACEI intolerant) and β-blockers Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent CV hospitalization, acute MI, elevated BNP or NT-proBNP level, or NYHA Class II to IV symptoms	ARB in addition to ACEI Hydralazine/isosorbide dinitrate combination if ARB or ACEI not tolerated/contraindicated Thiazide/thiazide-like or loop diuretics are recommended as additive therapy. DHP CCB can also be used A combined ARB/neprilysin inhibitor is recommended (in place of an ACEI or ARB) in symptomatic patients with HTN and HFrEF on standard guideline-based therapies	Titrate doses of ACEI and ARBs to those used in clinical trials Carefully monitor potassium and renal function if combining any of ACEI, ARB and/or aldosterone antagonist
Dyslipidemia	Does not affect initial treatment recommendations	Combination of additional agents	
DM with Albuminuria (ACR >2.0 mg/mmol renal disease, CVD or additional CV risk factors)	ACEI or ARB	Addition of a DHP CCB is preferred over a thiazide/ thiazide-like diuretic	A loop diuretic could be considered in hypertensive chronic kidney disease patients with extracellular fluid volume overload
DM without Albuminuria (criteria listed above)	ACEI, ARB, DHP CCB, or thiazide/ thiazide-like diuretics	Combination of first-line drugs If combination with ACEI is being considered, a DHP CCB is preferable to a thiazide/thiazide like diuretic	Normal urine ACR <2.0 mg/mmol
Non-Diabetic Chronic Kidney Disease with Proteinuria (urinary protein >500 mg/24 h or ACR >30 mg/mmol)	ACEI (ARB if ACEI intolerant), if there is proteinuria Diuretics as additive therapy	Combinations of additional agents	Patients on an ACEI or ARB should have careful monitoring of renal function and potassium. ACEI and ARB combinations are not recommended in patients without proteinuria
Renovascular Disease	Does not affect initial treatment recommendations Atherosclerotic renal artery stenosis should be primarily managed medically, while revascularization should be considered for renal fibromuscular dysplasia	Combinations of additional agents	Caution in using ACEI or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney Renal artery angioplasty and stenting could be considered for patients with renal artery stenosis and complicated, uncontrolled HTN

2020 Hypertension Highlights, Hypertension Canada.
https://hypertension.ca/wp-content/uploads/2018/07/Hypertension-Guidelines-English-2018-Web.pdf

Table 21. Common Antihypertensive Medications in Pregnancy and Lactation

Pregnancy			Lactation
First line oral drugs	**Second line oral drugs**	**Medications to avoid**	**Oral drugs**
Labetalol Methyldopa Long-acting oral nifedipine Other β-blockers (acebutolol, metoprolol, pindolol, and propranolol)	Clonidine Hydralazine Thiazide diuretics	ACEIs* ARBs*	Labetalol Methyldopa Long-acting oral nifedipine Enalapril Captopril

* Fetotoxicity of renal system

Follow-Up

- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification q3-6 mo
- pharmacological
  - follow-up q1-2 mo until BP under target for 2 consecutive visits, q3-6 mo once at target BP
  - follow-up frequently for patients with symptomatic/severe HTN, antihypertensive drug intolerance, target organ damage
- referral is indicated for cases of refractory HTN, suspected secondary causes, or worsening renal failure
- hospitalization is indicated for malignant HTN

Systematic Review for 2017 ACC/AHA Guidelines for Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults
Hypertension 2018;71:e116-135
Purpose: Determine evidence for self-measured BP without other augmentation for clinical outcomes and BP control. Determine optimal target for BP lowering during antihypertensive therapy in adults. Determine benefits and harms of different classes of antihypertensive drugs.
Methods: Systematic review and meta-analysis using PubMed and EMBASE.
Results: There is a modest but significant improvement in sBP in RCTs of self-measured BP vs. usual care at 6 but not 12 mo; may be a helpful adjunct to routine office care. sBP lowering to a target of <130 mmHg may reduce risk of several important outcomes including MI, stroke, heart failure, and major CV events. No class of medications (i.e. ACEI, ARBs, CCBs, or β-blockers) was significantly better than thiazides and thiazide-like diuretics as a first-line therapy for any outcome.
Conclusion: Self-measured BP is a useful adjunct in BP control. Target sBP <130. Thiazides, CCBs, β-blockers, ARBs, ACEI are to be used as first-line therapy with patient factors guiding choice.

Joint Pain

• see Rheumatology, RH2

History
•number of joints involved: monoarticular, oligoarticular, polyarticular
•inflammatory vs. non-inflammatory
•pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
•onset: acute vs. chronic (>6 wk)
•morning stiffness (duration) vs. worse at end of day with activity
• PMHx
  ▪ trauma, infection, medications (steroids, diuretics)
  ▪ comorbidities: DM, renal insufficiency (gout), psoriatic arthritis, myeloma, osteoporosis, and OA
  ▪ FMHx of arthritis, autoimmune disease
•ROS: constitutional symptoms (neoplasm, septic arthropathy), myalgia, skin/eye/nail/hand changes, and GI/GU changes

Signs and Symptoms of Inflammatory Arthritis

WARM(S) Joints
Worse with rest, better with activity
Awakening in the latter half of the night
Redness around joint
Morning stiffness (>30 min)
Soft tissue swelling, erythema

Physical Exam
• vitals
•specific joint exams to affected areas
•systemic features (skin, nails, eyes, hands)

Investigations (Guided by the History and Physical Exam)
•general: CBC and differential, electrolytes, Cr
•acute phase reactants: ESR, CRP
•complement (C3, C4)
•urinalysis to detect disease complications (proteinuria, active sediment)
•serology (tailored to clinical suspicion, see Rheumatology, RH4)
  ▪ antinuclear antibody (ANA), negative ANA helps to exclude SLE, positive ANA in subset of RA
  ▪ anti-double stranded DNA (anti-dsDNA), perform anti-dsDNA and anti-smith (anti-Sm) for SLE if positive ANA
  ▪ human leukocyte antigen B27 (HLA-B27), more consistent with reactive arthritis than RA
  ▪ anti-histidyl tRNA synthetase autoantibodies (anti-Jo1), positive in dermatomyositis and polymyositis
  ▪ anti-Sm, positive in SLE
  ▪ anti-La antibodies (anti-La), positive in Sjögren's disease
  ▪ anti-Sjögren's-syndrome-related antigen A (anti-SSA/Ro), positive in Sjögren's disease
  ▪ rheumatoid factor (RhF), positive in RA and other conditions including Sjögren's disease
  ▪ anti-cyclic citrullinated peptide (anti-CCP), positive in RA
•synovial fluid analysis (cell count and differential, culture, Gram stain, microscopy)
•radiology (plain film, CT, MRI, U/S, bone densitometry, bone scan)

Systemic Features
- Fever (SLE, infection)
- Rash (SLE, psoriatic arthritis)
- Nail abnormalities (psoriatic, reactive arthritis)
- Uveitis (psoriatic, reactive arthritis, ankylosing spondylitis)
- Myalgias (fibromyalgia, myopathy)
- Weakness (polymyositis, neuropathy)
- GI symptoms (scleroderma, IBD)
- GU symptoms (reactive arthritis, gonococcemia)

Treatment
•tailor therapy depending on the specific cause; consider referral to rheumatologist
•non-pharmacological: patient education, lifestyle modification, assisted devices, physiotherapy, occupational therapy
•pharmacological: analgesia (acetaminophen, NSAIDs), anti-inflammatory (disease-modifying anti-rheumatic drugs (DMARDs), steroids, antibiotics
  ▪ if OA, consider steroid injections, hyaluronic acid injections

Low Back Pain

• see Orthopedic Surgery, OR27
•Clinically Organized Relevant Exam (CORE) Back Tool: https://cep.health/clinical-products/low-back-pain/

Definition
•acute: <6 wk
•subacute: 6-12 wk
•chronic: >12 wk

Epidemiology
•5th most common reason for visiting a physician
•lifetime prevalence: 90%, peak prevalence: ages 45-60
•largest WSIB category and most common cause of chronic disability for individuals <45 y/o
•90% resolve in 6 wk, <5% become chronic

Etiology

- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes (worse with movement, better with rest)
  - soft tissue: sprain (ligament), strain (muscle)
  - spine: facet joint/disc degeneration, disc herniation, spinal stenosis (e.g. spondylosis), spondylolisthesis, compression fracture
  - other: pregnancy
- 2% are non-mechanical causes
  - surgical emergencies
    - cauda equina syndrome (areflexia, lower extremity weakness, saddle anaesthesia, fecal incontinence, urinary retention)
- medical conditions
    - neoplastic: primary, metastatic, multiple myeloma
    - infectious: osteomyelitis, TB
    - metabolic: osteoporosis, osteomalacia, Paget's disease
    - rheumatologic: ankylosing spondylitis, polymyalgia rheumatica
    - referred pain: perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster
    - abdominal aortic aneurysm (pulsatile abdominal mass)

Physical Exam

- inspection: curvature, posture, gait
- palpation: bony deformities/tenderness, paraspinal muscle bulk/tenderness, trigger points
  - percussion of spine to elicit pain due to fracture or infection
- range of motion and peripheral pulses
- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes, sensation)
- special tests
  - straight leg raise (positive if pain at <70° and aggravated by ankle dorsiflexion), positive test is indicative of sciatica/lumbosacral nerve root irritation
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy

Investigations
- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI

Table 22. Approach to Non-Traumatic Low Back Pain

	Back Dominant (Pain greatest above gluteal fold)		Leg Dominant (Pain greatest below gluteal fold)	
History	**Pattern 1** Worse with flexion Constant/intermittent	**Pattern 2** Worse with extension Never worse with flexion Always intermittent	**Pattern 3** Pain changes with back movement/position Currently/previously constant	**Pattern 4** Worse with activity Improves with rest and posture change Intermittent/short duration
Physical Exam	Normal neurological exam Fast responder Improves with extension Slow responder No change or worsens with extension	Normal neurological exam ± improves with flexion Worse with extension	Leg pain can improve but not disappear Positive straight leg raise ± conduction loss Fast responder Improves with specific back position Slow responder Not better with position changes	No irritative findings ± conduction loss
Likely Pathology	Disc pain	Facet joint pain	Compressed nerve pain: sciatica	Symptomatic spinal stenosis: neurogenic claudication
Initial Management	Scheduled extension Lumbar roll Night lumbar roll Medication as required: acetaminophen + NSAIDs	Scheduled flexion Limited extension Night lumbar roll Medication as required: acetaminophen + NSAIDs	Prone extension Supine "Z" lie Lumbar roll Night lumbar roll Medication as required: acetaminophen + NSAIDs, may consider opioid therapies if 1st line not sufficient	Abdominal exercises Night lumbar roll Sustained flexion Pelvic tilt Medication as required: acetaminophen + NSAIDs

Adapted from: American Academy of Orthopaedic Surgeons. Acute care: nontraumatic low back pain. Orthopaedic Knowledge Update: Spine 2 2001;153-166
Adapted from: Centre for Effective Practice. Clinically Organized Relevant Exam (CORE) Back Tool. 2016

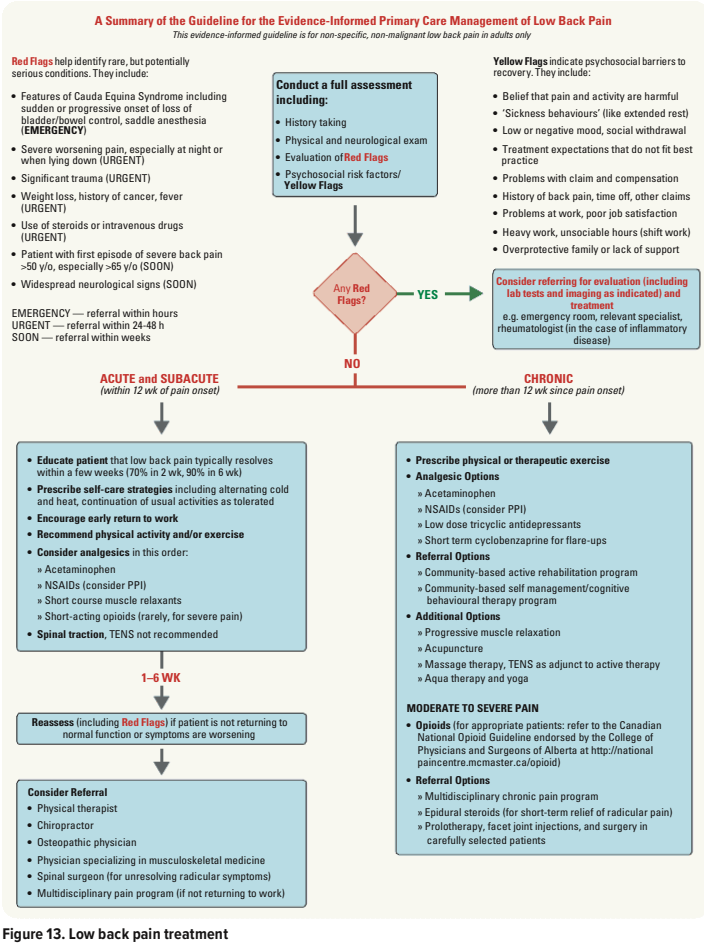

A Summary of the Guideline for the Evidence-Informed Primary Care Management of Low Back Pain
This evidence-informed guideline is for non-specific, non-malignant low back pain in adults only
Red Flags help identify rare, but potentially serious conditions. They include:
• Features of Cauda Equina Syndrome including sudden or progressive onset of loss of bladder/bowel control, saddle anesthesia (EMERGENCY)
• Severe worsening pain, especially at night or when lying down (URGENT)
• Significant trauma (URGENT)
• Weight loss, history of cancer, fever (URGENT)
• Use of steroids or intravenous drugs (URGENT)
• Patient with first episode of severe back pain >50 y/o, especially >65 y/o (SOON)
• Widespread neurological signs (SOON)
EMERGENCY — referral within hours
URGENT — referral within 24-48 h
SOON — referral within weeks
Conduct a full assessment including:
• History taking
• Physical and neurological exam
• Evaluation of Red Flags
• Psychosocial risk factors/ Yellow Flags
Yellow Flags indicate psychosocial barriers to recovery. They include:
• Belief that pain and activity are harmful
• 'Sickness behaviours' (like extended rest)
• Low or negative mood, social withdrawal
• Treatment expectations that do not fit best practice
• Problems with claim and compensation
• History of back pain, time off, other claims
• Problems at work, poor job satisfaction
• Heavy work, unsociable hours (shift work)
• Overprotective family or lack of support
Any Red Flags?
YES
Consider referring for evaluation (including lab tests and imaging as indicated) and treatment
e.g. emergency room, relevant specialist, rheumatologist (in the case of inflammatory disease)
NO
ACUTE and SUBACUTE
(within 12 wk of pain onset)
CHRONIC
(more than 12 wk since pain onset)
• Educate patient that low back pain typically resolves within a few weeks (70% in 2 wk, 90% in 6 wk)
• Prescribe self-care strategies including alternating cold and heat, continuation of usual activities as tolerated
• Encourage early return to work
• Recommend physical activity and/or exercise
• Consider analgesics in this order:
» Acetaminophen
» NSAIDs (consider PPI)
» Short course muscle relaxants
» Short-acting opioids (rarely, for severe pain)
• Spinal traction, TENS not recommended
1–6 WK
Reassess (including Red Flags) if patient is not returning to normal function or symptoms are worsening
Consider Referral
• Physical therapist
• Chiropractor
• Osteopathic physician
• Physician specializing in musculoskeletal medicine
• Spinal surgeon (for unresolving radicular symptoms)
• Multidisciplinary pain program (if not returning to work)
• Prescribe physical or therapeutic exercise
• Analgesic Options
» Acetaminophen
» NSAIDs (consider PPI)
» Low dose tricyclic antidepressants
» Short term cyclobenzaprine for flare-ups
• Referral Options
» Community-based active rehabilitation program
» Community-based self management/cognitive behavioural therapy program
• Additional Options
» Progressive muscle relaxation
» Acupuncture
» Massage therapy, TENS as adjunct to active therapy
» Aqua therapy and yoga
MODERATE TO SEVERE PAIN
• Opioids (for appropriate patients: refer to the Canadian National Opioid Guideline endorsed by the College of Physicians and Surgeons of Alberta at http://national paincentre.mcmaster.ca/opioid)
• Referral Options
» Multidisciplinary chronic pain program
» Epidural steroids (for short-term relief of radicular pain)
» Prolotherapy, facet joint injections, and surgery in carefully selected patients

Figure 13. Low back pain treatment
Adapted with permission from Toward Optimized Practice (TOP) Low Back Pain Working Group. 2015 December. Evidence-informed primary care management of low back pain: Clinical practice guideline. Edmonton, AB: Toward Optimized Practice. Appendix I – Summary, p. 43-44. Available from: https://actt.albertadoctors.org/CP6s/Pages/Low-Back-Pain.aspx. Copyright 2015, Toward Optimized Practice.

Massage for Low Back Pain
Cochrane DB Syst Rev 2015;4
Purpose: To evaluate the effect of massage therapy for non-specific low back pain.
Methods: Meta-analysis of randomized or quasi-randomized trials evaluating use of any massage modality (hands or mechanical device) as a treatment for non-specific low back pain.
Results: 13 RCTs were identified, comparing massage therapy to other active or sham treatments. Massage was superior for pain and function on both short- and long-term follow-ups relative to sham treatment. It was similar to exercises, and superior to join mobilization, relaxation therapy, physical therapy, acupuncture and self-care education. Benefits lasted at least 1 yr post-treatment. Acupuncture massage was associated with better results than classic (Swedish) massage, and Thai massage produced similar results to the classic massage.
Conclusions: Massage may be beneficial for subacute and chronic non-specific low back pain, especially in combination with exercise and education.

Association of Spinal Manipulative Therapy with Clinical Benefit and Harm for Acute Low Back Pain
JAMA 2017;317:1451-1460
Purpose: To systematically review studies about the effectiveness and harms of Spinal Manipulative Therapy (SMT) for acute (≤6 wk) low back pain.
Methods: Systematic review and meta-analysis including RCTs and observational studies. Evidence assessed using GRADE criteria. Outcomes such as pain, function, or any harms were measured during 6 wk of SMT.
Results: 15 RCTs provided moderate-quality evidence that SMT has a statistically significant association with improvements in pain (pooled mean improvement in the 100 mm visual analog pain scale, −9.95 (95% CI, −15.6 to −4.3)). 12 RCTs (1381 patients) produced moderate-quality evidence that SMT has a statistically significant association with improvements in function (pooled mean effect size, −0.39 (95% CI, −0.71 to −0.07)). No RCT reported any serious adverse event. Minor transient adverse events such as increased pain, muscle stiffness, and headache were reported 50-67% of the time in large case series of patients treated with SMT.
Conclusion: SMT in acute low back pain was associated with modest improvements in pain and function at up to 6 wk, with transient minor MSK harms. However, heterogeneity in study results was large.

Menopause/Hormone Therapy

• see Gynecology, GY36

Definition
• 12 mo of amenorrhea following the final menstrual period

Epidemiology
• mean age of menopause is 51.4 yr

Clinical Features
• associated with estrogen deprivation
• urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
• vascular: vasomotor instability (e.g. hot flashes), increased risk of heart disease
• bones: bone loss, joint/muscle/back pain, fractures, loss of height
• brain: depression, irritability, mood swings, memory loss

Management
- person-specific support and offering of health education about menopause (if desired)
- https://www.menopauseandu.ca
- non-pharmacological management: encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1200 mg/d) and vitamin D (1000 IU/d)
- pharmacological management:
  - hormone therapy (HT)
    - initiation of HT requires a thorough discussion of short- and long-term benefits and risks
o HT should not be initiated if >10y post-menopause
    - regimens: cyclic or continuous estrogen-progestin, estrogen only (if no uterus, patch/gel/cream/ring/vaginal tablet)
    - advantages: decreases risk of osteoporotic fractures, CRC
    - disadvantages: increases risk of DVT and PE. Can increase risk of breast cancer and stroke if HT is initiated >60 yr old or >10 yr from menopause
  - venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

Osteoarthritis

- see Rheumatology, RH5

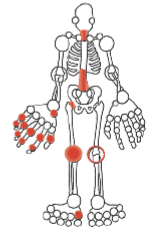
Definition
- progressive deterioration of articular cartilage and surrounding joint structures caused by genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation

Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone >65 yr shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, periarticular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (through occupational therapy/physiotherapy), assistive devices (e.g. canes, orthotics)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs (cyclooxygenase-2 (COX2) selective) in low doses for short durations
  - 3rd line: duloxetine, combination analgesics (e.g. acetaminophen and codeine)
  - other pharmacological adjuncts:
    - intra-articular corticosteroid or hyaluronic acid injections
    - topical NSAIDS (diclofenac)
    - capsaicin cream
    - oral glucosamine (evidence remains inconclusive)
- surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)



- Hand (DIP, PIP, 1st CMC)
- Hip
- Knee
- 1st MTP
- L-spine (L4-L5, L5-S1)
- C-spine
- Uncommon: ankle, shoulder, elbow, MCP, rest of wrist

© Linda Colati

Figure 14. Common sites of involvement in OA
CMC = carpometacarpal joint
DIP = distal interphalangeal joint
MCP = metacarpophalangeal joint
MTP = metatarsophalangeal joint
PIP = proximal interphalangeal joint

Osteoporosis

- see Endocrinology, E46
- for current guidelines and tools see www.osteoporosis.ca

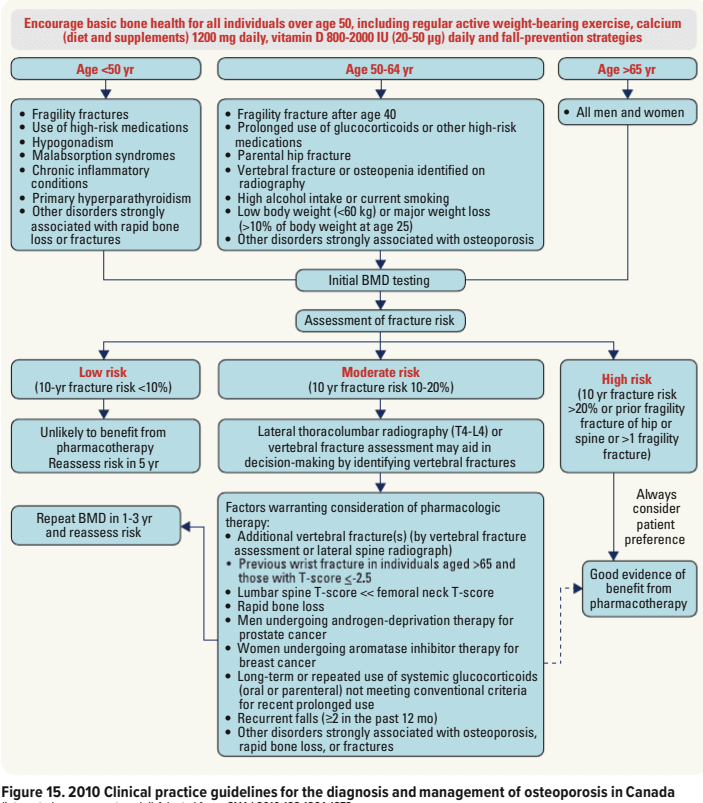

Encourage basic bone health for all individuals over age 50, including regular active weight-bearing exercise, calcium (diet and supplements) 1200 mg daily, vitamin D 800-2000 IU (20-50 µg) daily and fall-prevention strategies
Age <50 yr
Age 50-64 yr
Age >65 yr
• Fragility fractures
• Use of high-risk medications
• Hypogonadism
• Malabsorption syndromes
• Chronic inflammatory conditions
• Primary hyperparathyroidism
• Other disorders strongly associated with rapid bone loss or fractures
• Fragility fracture after age 40
• Prolonged use of glucocorticoids or other high-risk medications
• Parental hip fracture
• Vertebral fracture or osteopenia identified on radiography
• High alcohol intake or current smoking
• Low body weight (<60 kg) or major weight loss (>10% of body weight at age 25)
• Other disorders strongly associated with osteoporosis
• All men and women
Initial BMD testing
Assessment of fracture risk
Low risk
(10-yr fracture risk <10%)
Moderate risk
(10 yr fracture risk 10-20%)
High risk
(10 yr fracture risk >20% or prior fragility fracture of hip or spine or >1 fragility fracture)
Unlikely to benefit from pharmacotherapy
Reassess risk in 5 yr
Lateral thoracolumbar radiography (T4-L4) or vertebral fracture assessment may aid in decision-making by identifying vertebral fractures
Always consider patient preference
Repeat BMD in 1-3 yr and reassess risk
Factors warranting consideration of pharmacologic therapy:
• Additional vertebral fracture(s) (by vertebral fracture assessment or lateral spine radiograph)
• Previous wrist fracture in individuals aged >65 and those with T-score ≤-2.5
• Lumbar spine T-score << femoral neck T-score
• Rapid bone loss
• Men undergoing androgen-deprivation therapy for prostate cancer
• Women undergoing aromatase inhibitor therapy for breast cancer
• Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use
• Recurrent falls (≥2 in the past 12 mo)
• Other disorders strongly associated with osteoporosis, rapid bone loss, or fractures
Good evidence of benefit from pharmacotherapy

Figure 15. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada
(integrated management model) Adapted from: CMAJ 2010;182:1864-1873

Definition
- age-related disease characterized by decreased bone mass and increased susceptibility to fractures

Epidemiology
- in Canada, affects 1 in 4 women and 1 in 8 men

Clinical Presentation
- asymptomatic for many years
- fragility or osteoporotic fractures

Approach to Clinical Assessment
- identify risk factors on history and physical examination
- history
  - prior falls, fragility fractures, parental hip fractures, and gait or balance issues
  - glucocorticoid use
  - smoking and alcohol intake (≥3 units/d)
  - RA
- physical examination
  - height annually (prospective loss >2 cm or historical loss >6 cm) and weight (weight loss >10% since age 25)
  - rib-to-pelvis distance ≤2 fingers' breadth

Disorders Strongly Associated with Osteoporosis Include:
Primary hyperparathyroidism, T1DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. IBD)

10 Yr Fracture Risk Assessment
FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population
FRAX and CAROC are available online from: https://osteoporosis.ca/tools/

How Much Calcium Do We Need?

Age	Amount/day
4-8	1000 mg
9-18	1300 mg
19-50	1000 mg
>50	1200 mg

Calcium Content of Common Foods
1 cup milk = 300 mg
¾ cup yogurt = 332 mg
½ can salmon with bones = 240 mg
½ cup cooked broccoli = 33 mg
1 medium orange = 50 mg

Vitamin D Content in Food
- Milk fortified with vitamin D3 contains 100 IU per 250 mL glass
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish, and fish oils (halibut and cod liver oils) all contain small amounts; supplementation is necessary to obtain adequate levels as dietary intake has minimal impact
- Most multivitamins provide 400 IU of vitamin D3
- Recommended daily intake of vitamin D:
  - adults 19-50 years old, including women who are pregnant or breastfeeding: 400-1000 IU daily
  - individuals over 50 years, or younger people who have risk factors (osteoporosis, multiple fractures, or conditions affecting the absorption of vitamin D): 800-2000 IU daily

- occiput-to-wall distance >5 cm
- assess fall risk by ability to get up from chair without support with arms, and walking several steps and return

Investigations
- CBC, Cr, corrected Ca $^{2+}$, ALP, TSH, 25-hydroxyvitamin D (after 3-4 mo of adequate supplementation), and serum protein electrophoresis if there are vertebral fractures

Indications for Bone Mineral Density Testing and Management
- see Endocrinology, E47
- see *Figure 15, FM45*

Rash

- see Dermatology, D16

Sexually Transmitted Infections

- see Gynecology, GY29

Definition
- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

Epidemiology
- high incidence rates worldwide
- canadian prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes
  - less common: hepatitis B, HIV, syphilis, trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venereum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

History
- sexual Hx
  - age of first intercourse, gender of sexual partners (past and present), sexual activity (oral, anal, vaginal intercourse, use of sex toys), contraception use, sexual activity during travel
  - total number of partners in the past year and duration of involvement with each
- STI Hx
  - STI awareness, previous STIs and testing (including Pap tests), partner communication/history regarding STIs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

Investigations/Screening
- individuals at increased risk should be screened for hepatitis B, HIV, and syphilis
- Pap test q3 yr for anyone with a cervix aged 25 to 69 who has ever been sexually active
- annual screening for all sexually active people under 30 for gonorrhea and chlamydia

Management
- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune
- offer Gardasil® to:
  - females between ages of 9 to 27
  - women ≥27 if at risk of ongoing exposure
  - males between ages 9 to 27 to prevent anogenital cancer and genital warts
  - ≥27 years of age and who are at risk of ongoing exposure source
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use barrier contraception or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- a person with an STI is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients diagnosed with bacterial STI or trichomonas infection should abstain from sexual activity until treatment completion and for 7 d after treatment for both partners, or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis, chancroid

When an STI is detected in a child, evaluation for sexual abuse is mandatory

STI Risk Factors

Sexually active males and females <25 yr old

Unprotected sex, sexual contact with a known case of STI, previous STI

New sexual partner or >2 sexual partners in the past 12 mo

Street involved, homeless, and/or substance misuse

Sexual History
5 P's
Partners (numbers, gender)
Practices (vaginal, oral, anal insertive/receptive)
Protection
Past history of STIs
Pregnancy prevention

Efficacy of Human Papillomavirus Vaccines – A Systematic Quantitative Review
Int J Gynecol Cancer 2009;19:1166-1176
Purpose: To evaluate two vaccines for HPV in terms of efficacy, safety and immunogenicity.
Methods: Systematic review of RCTs involving women between the ages of 9 and 26 yr, randomly assigned to receive vaccination with HPV L1 virus-like particle in either quadrivalent (HPV 6, 11, 16, 18), bivalent (HPV 16, 18), or univalent (HPV 16) form or placebo. Main outcomes were prevention of cytologically and/or histologically proven lesions (including LSIL, HSIL, VIN, VAIN, AIN, adenocarcinoma *in situ* of the cervix, or cancer of the cervix associated with HPV infection).
Results: Six studies involving 47236 women were included. Bivalent and quadrivalent vaccines reduced the rate of lesions in the cervix, vulva, vagina, and anogenital region with efficacy of 93% (95% CI 87-96%) and 62% (95% CI 27-70%), respectively. More symptoms were found in the bivalent vaccine group (35%, 5-73%) compared to control groups.
Conclusion: Prophylactic vaccination can prevent HPV infection in women ages 9-26 not previously infected with HPV subtypes covered by the vaccines.

Table 23. Diagnosis and Treatment of Common STIs

	Signs and Symptoms	Investigations	Treatment	Complications
Gonococcal Urethritis/ Cervicitis (*Neisseria gonorrhoeae*)	M: urethral discharge, unexplained pyuria, dysuria, irritation, testicular swelling or pain, symptoms of epididymitis F: mucopurulent endocervical discharge, vaginal bleeding, dysuria, pelvic pain, dyspareunia M and F: often asymptomatic, can involve rectal symptoms in cases of unprotected anal sex	M: first-void urine nucleic acid amplification test (NAAT), urethral swab for Gram stain and culture F: vaginal swab or urine NAAT, endocervical swab for Gram stain and culture, vaginal swab for wet mount (to rule out trichomonas) M and F: urine NAAT, rectal/pharyngeal swabs if indicated	Ceftriaxone 500 mg IM single dose* Test of cure: cultures 3-7 d post-treatment for pharyngeal infections, ongoing signs or symptoms, treatment failure, or pregnancy Repeat screening in all patients 6 mo post-treatment	M: urethral strictures, epididymitis, infertility F: PID, infertility, ectopic pregnancy, perinatal infection, chronic pelvic pain M and F: arthritis, increased risk of acquiring and transmitting HIV
Non-Gonococcal Urethritis/Cervicitis (Usually *Chlamydia trachomatis*)**	~70% asymptomatic If symptoms appear (usually 2-6 wk after infection) then similar to gonococcal symptoms (see above)	Same as above	Doxycycline 100 mg PO BID x7 d + gonococcal urethritis/cervicitis prescription* Repeat screening in all patients 3 mo post-treatment	Same as above
Human Papillomavirus (genital warts, cervical dysplasia)	Most are asymptomatic M: cauliflower lesions (condylomata acuminata) on skin/mucosa of penile or anal area F: cauliflower lesions and/or pre-neoplastic/neoplastic lesions on cervix/vagina/vulva	None needed if simple condylomata Potential biopsy of suspicious lesions F: screening for cervical dysplasia through regular Pap smears	For condylomata: cryotherapy, electrocautery, laser excision, topical therapy (patient-applied or office-based) For cervical dysplasia: colposcopy and possible excision, dependent on grade of lesion	M and F: anal cancer MSM and F who have receptive anal sex: rectal cancer F: cervical/vaginal/vulvar cancer
Genital Herpes (HSV-1 and -2)	1° episode: painful vesiculoulcerative genital lesions ± fever, tender lymphadenopathy, protracted course Recurrent episodes: less extensive lesions, shorter course may have "trigger factors"	Swab of vesicular content for culture or NAAT	1° Episode Acyclovir 400 mg PO TID daily x7-10 d or Famciclovir 250 mg PO TID x7-10 d or Valacyclovir 1000 mg PO BID x7-10 d Recurrent Episode Acyclovir 800 mg PO TID daily x2 d or 800 mg PO BID x5 d Famciclovir 1000 mg PO BID x 1 d or 125 mg PO BID × 5d or 500 mg PO once followed by 250 mg PO BID x5 d Valacyclovir 500 mg PO BID x3 d or 1000 mg PO once daily x5 d	Genital pain, urethritis, cervicitis, aseptic meningitis, increased risk of acquiring and transmitting HIV
Infectious Syphilis (*Treponema pallidum*)	1°: chancre (painless sore), regional lymphadenopathy 2°: rash and flu-like symptoms, meningitis, headache, uveitis, retinitis, condyloma lata, mucous lesions, alopecia Latent Phase: asymptomatic 3°: neurologic, cardiovascular, and tissue complications	Specimen collection from 1° and 2° lesions, screen high-risk individuals with serologic syphilis testing (VDRL), universal screening of pregnant women	Benzathine penicillin G 2.4 million units IM single dose For late latent, syphilis, 2.4 million units IM penicillin G once a week x3 wk Notify partners (last 3-12 mo) Continuous follow-up and testing until patients are seronegative	Chronic neurologic and cardiovascular sequelae, increased risk of acquiring and transmitting HIV

F = females; M = males
*N.B. if urethritis/cervicitis is suspected, always treat for both gonococcal and nongonococcal types (i.e. ceftriaxone AND azithromycin)
**Most common reportable STI in Canada

Sinusitis

• see Otolaryngology, OT25

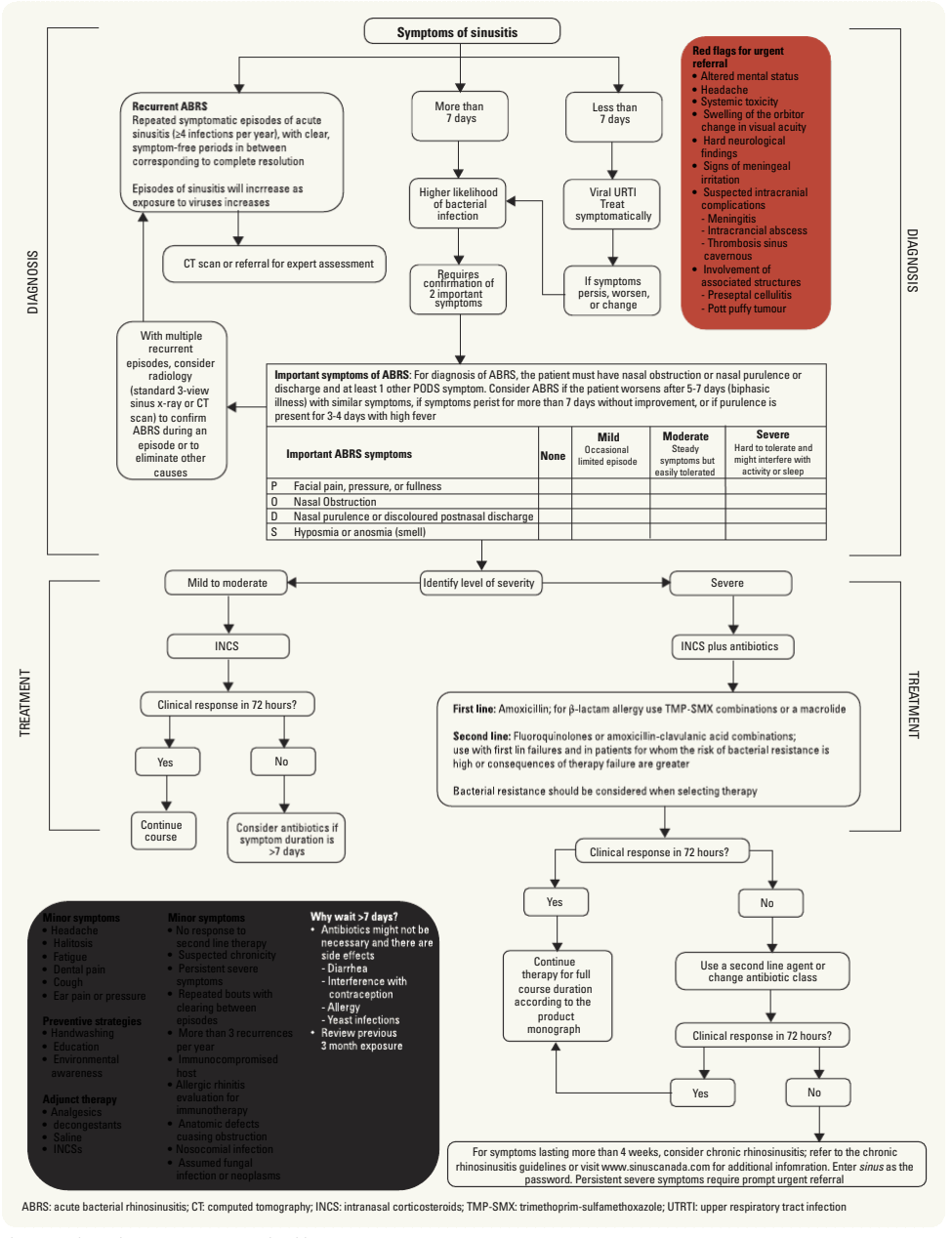
Definition
• acute or chronic inflammation of the sinuses, often also involving the nasal cavities

Etiology
• viral etiology is more common
• viral: rhinovirus, influenza, parainfluenza
• bacterial: *S. pneumoniae, H. influenzae, M. catarrhalis*

Clinical Presentation
• often presents with PODS(facial Pain, pressure, or fullness; nasal Obstruction; nasal purulence or discoloured postnasal Discharge; and Smell disorder), symptoms (see *Figure 16, FM48*)

Management of Acute Sinusitis
• for symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical or oral decongestants
• antihistamines are ineffective
• mild to moderate acute bacterial sinusitis: intranasal corticosteroids
• severe acute bacterial sinusitis: antibiotics and intranasal corticosteroids
  - first-line antibiotic is amoxicillin, and second line may include amoxicillin-clavulanic acid or a fluoroquinolone
  - ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, or ≥4 episodes/yr, refer urgently for the red flags listed in the sidebar

Red Flags for Urgent Referral
- Altered mental status
- Headache
- Systemic toxicity
- Swelling of the orbit or change in visual acuity or extraocular muscles
- Hard neurological findings
- Signs of meningeal irritation
- Suspected intracranial complications (meningitis, intracranial abscess, cavernous sinus thrombosis)
- Involvement of associated structures (periorbital cellulitis, Pott's puffy tumour)


DIAGNOSIS
Symptoms of sinusitis
Recurrent ABRS
Repeated symptomatic episodes of acute sinusitis (≥4 infections per year), with clear, symptom-free periods in between corresponding to complete resolution
Episodes of sinusitis will increase as exposure to viruses increases
CT scan or referral for expert assessment
With multiple recurrent episodes, consider radiology (standard 3-view sinus x-ray or CT scan) to confirm ABRS during an episode or to eliminate other causes
More than 7 days
Less than 7 days
Higher likelihood of bacterial infection
Requires confirmation of 2 important symptoms
Viral URTI Treat symptomatically
If symptoms persis, worsen, or change
Red flags for urgent referral
• Altered mental status
• Headache
• Systemic toxicity
• Swelling of the orbitor change in visual acuity
• Hard neurological findings
• Signs of meningeal irritation
• Suspected intracranial complications
- Meningitis
- Intracrancial abscess
- Thrombosis sinus cavernous
• Involvement of associated structures
- Preseptal cellulitis
- Pott puffy tumour
Important symptoms of ABRS: For diagnosis of ABRS, the patient must have nasal obstruction or nasal purulence or discharge and at least 1 other PODS symptom. Consider ABRS if the patient worsens after 5-7 days (biphasic illness) with similar symptoms, if symptoms perist for more than 7 days without improvement, or if purulence is present for 3-4 days with high fever
Important ABRS symptoms | None | Mild Occasional limited episode | Moderate Steady symptoms but easily tolerated | Severe Hard to tolerate and might interfere with activity or sleep
P Facial pain, pressure, or fullness
O Nasal Obstruction
D Nasal purulence or discoloured postnasal discharge
S Hyposmia or anosmia (smell)
TREATMENT
Identify level of severity
Mild to moderate
Severe
INCS
INCS plus antibiotics
Clinical response in 72 hours?
Yes
No
Continue course
Consider antibiotics if symptom duration is >7 days
First line: Amoxicillin; for β-lactam allergy use TMP-SMX combinations or a macrolide
Second line: Fluoroquinolones or amoxicillin-clavulanic acid combinations; use with first lin failures and in patients for whom the risk of bacterial resistance is high or consequences of therapy failure are greater
Bacterial resistance should be considered when selecting therapy
Clinical response in 72 hours?
Yes
No
Continue therapy for full course duration according to the product monograph
Use a second line agent or change antibiotic class
Clinical response in 72 hours?
Yes
No
For symptoms lasting more than 4 weeks, consider chronic rhinosinusitis; refer to the chronic rhinosinusitis guidelines or visit www.sinuscanada.com for additional infomration. Enter sinus as the password. Persistent severe symptoms require prompt urgent referral
Minor symptoms
• Headache
• Halitosis
• Fatigue
• Dental pain
• Cough
• Ear pain or pressure
Preventive strategies
• Handwashing
• Education
• Environmental awareness
Adjunct therapy
• Analgesics
• decongestants
• Saline
• INCSs
Minor symptoms
• No response to second line therapy
• Suspected chronicity
• Persistent severe symptoms
• Repeated bouts with clearing between episodes
• More than 3 recurrences per year
• Immunocompromised host
• Allergic rhinitis evaluation for immunotherapy
• Anatomic defects cuasing obstruction
• Nosocomial infection
• Assumed fungal infection or neoplasms
Why wait >7 days?
• Antibiotics might not be necessary and there are side effects
- Diarrhea
- Interference with contraception
- Allergy
- Yeast infections
• Review previous 3 month exposure

ABRS: acute bacterial rhinosinusitis; CT: computed tomography; INCS: intranasal corticosteroids; TMP-SMX: trimethoprim-sulfamethoxazole; UTRTI: upper respiratory tract infection

Figure 16. Diagnosis and management of sinusitis
ABRS = acute bacterial rhinosinusitis
Adapted from: Kaplan A. Canadian guidelines for acute bacterial rhinosinusitis. Can Fam Physician. 2014 Mar;60(3).

Sleep Disorders

• see Respirology, R29 and Neurology, N48

Definition and Clinical Presentation

- most often characterized by one of three complaints: insomnia, parasomnias, excessive daytime sleepiness
- insomnia: difficulty falling asleep, difficulty maintaining sleep, early morning wakening, non-refreshing sleep
- parasomnias: night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
- excessive daytime sleepiness: abnormal fatigue or tiredness extending into waking hours

Epidemiology

- 1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems

Etiology

- primary sleep disorders
  - primary insomnia, narcolepsy, OSA, restless leg syndrome, periodic limb movements of sleep
- secondary causes
  - medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD, pregnancy, neurological disorders
  - drugs: alcohol, caffeine, nicotine, nicotine replacement therapy, β-agonists, antidepressants, steroids, decongestants, amphetamine, cocaine, modafinil, - acetylcholinesterase inhibitors, dopamine agonists, and others
  - psychiatric: mood and anxiety disorders
  - lifestyle factors: shift work, jet lag

Risk Factors for OSA

- Male gender
- Obesity (due to upper airway narrowing). BMI >28 kg/m2 present in 60-90% of cases
- Children (commonly due to large tonsils and adenoids)
- Aging (due to decreased muscle tone)
- Persistent URTIs, allergies, nasal tumours, hypothyroidism (due to macroglossia), neuromuscular disease
- FMHx

Investigations

- complete sleep diary every morning for 1-2 wk, see https://app.consensussleepdiary.com/#/
  - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (e.g. CBC and differential, TSH)
- refer for sleep study, nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

Management of Specific Problems

- primary insomnia
  - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
  - consider asking the patient if they have questions or fears about sleep that you might be able to address
  - treat any suspected medical or psychiatric cause
  - exercise regularly, avoid heavy exercise within 3 h of bedtime
  - first-line treatment (CBT)
    - sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
    - relaxation therapy: deep breathing, meditation, biofeedback
    - stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
    - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient
    - address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
  - pharmacologic treatment (used to supplement CBT; short-term prescription of <14 d with appropriate follow-up in 7-14 d):
    - short-acting benzodiazepines (e.g. lorazepam) are used cautiously in exceptional circumstances, due to the risk of dependence, to:
      - break the cycle of chronic insomnia
      - manage an exacerbation of previously controlled insomnia
    - non-benzodiazepines: zopiclone, zolpidem, melatonin, sedating antidepressants (e.g. amitriptyline, trazodone)
    - if no progress or limited improvement on pharmacotherapy, consider referral to sleep medicine program
- snoring
  - results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  - physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)

- treatment
  - sleep on side (position therapy), weight loss
  - nasal dilators, tongue-retaining devices, mandibular advancement devices
- at risk of developing OSA

- OSA
  - apnea (no breathing for ≥10 s) resulting from partial or complete upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present
  - leads to a distinctive snorting, choking, awakening-type pattern as the body rouses itself to open the airway
  - apneic episodes can last from 20-180 s and occur 100-600 episodes/night
  - diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes/h of sleep
  - consequences
    - daytime somnolence, non-restorative sleep
    - poor social and work performance
    - mood changes: anxiety, irritability, depression
    - sexual dysfunction: poor libido, impotence
    - morning headache (due to hypercapnia)
    - HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
    - OSA is an independent risk factor for CAD
    - pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
    - memory loss, decreased concentration, confusion
  - investigations
    - evaluate BP, inspect nose, and oropharynx (enlarged adenoids or tonsils)
    - blood gas not helpful, TSH if clinically indicated
    - nocturnal polysomnography
  - treatment
    - modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
    - primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
    - surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy, and adenoidectomy (in children)
    - report patient to Ministry of Transportation if OSA is not controlled by CPAP

Sore Throat (Pharyngitis)

Definition

- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

Etiology

- viral: adenovirus, rhinovirus, influenza virus, RSV, Epstein-Barr virus (EBV), coxsackie virus, herpes simplex virus, cytomegalovirus (CMV), HIV
- bacterial: β-hemolytic *Streptococcus, Neisseria gonorrhoeae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Corynebacterium diphtheriae, Fusobacterium necrophorum*

Epidemiology

- viral
  - most common cause (90% in adults is viral), occurs year round
- bacterial
  - Group A β-hemolytic *Streptococcus* (GABHS)
    - most common bacterial cause
    - occurs most often in winter months
    - 5-15% of adult cases and up to 30-40% of all pediatric cases of acute pharyngitis
    - most prevalent between 5-17 yr old

Clinical Presentation

- viral
  - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  - nonspecific flu-like symptoms such as fever, malaise, and myalgia
  - often mimics bacterial infection
  - common viral infections
    - EBV (infectious mononucleosis)
      - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
    - coxsackie virus (hand, foot, and mouth disease)
      - primarily late summer, early fall
      - sudden onset of fever, pharyngitis, headache, abdominal pain, and vomiting

Red Flags in Patients with "Sore Throat"
- Persistence of symptoms longer than 1 wk without improvement
- Respiratory difficulty (particularly stridor, croup, etc.)
- Difficulty in handling secretions (peritonsillar abscess)
- Difficulty in swallowing (Ludwig's angina)
- Severe pain in the absence of erythema (supraglottitis/epiglottitis)
- Palpable mass (neoplasm)
- Blood in the pharynx or ear (trauma)

  - appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
  - ulcers are pale grey and several mm in diameter, have surrounding erythema, and may appear on hands and feet
- herpes simplex virus
  - like coxsackie virus, but ulcers are fewer and larger
  - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash

- bacterial
  - symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
  - signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
  - complications:
    - suppurative: abscess, sinusitis, otitis media, cervical adenitis, pneumonia
    - nonsuppurative: acute rheumatic fever, acute glomerulonephritis

Table 24. Modified Centor Score: Approach to Diagnosis and Management of GABHS

Criteria		Points
Cough absent?		1
History of fever >38°C?		1
Tonsillar exudate?		1
Swollen, tender anterior nodes?		1
Ages 5-14		1
Ages 15-44		0
Ages >45		–1
In communities with moderate levels of strep infection (10-20% of sore throats):		
Score	**0-2**	**3 or more**
Risk of GABHS	1-17%	28-53%
Suggested action	No further testing or antibiotics	Perform rapid antigen detection test (RADT) and treat with ABx if positive. For negative RADT and patient <20 yr, perform throat culture and treat with ABx if culture is positive. For negative RADT and patients ≥20 yr, no ABx should be given

Note: Patients who score 2 points should undergo RADT if they are under 18, immunocompromised, frail, or otherwise clinically unwell
Limitations:
*This score is not applicable to patients <5 yr
*If an outbreak or epidemic of illness caused by GABHS is occurring in any community, the score is invalid and should not be used
Adapted from: Centor RM, et al. Med Decis Making 1981;1:239-46; Sykes EA, et al. Can Fam Physician. 2020 Apr; 66(4): 251-257.

Investigations

- suspected GABHS
  - see *Table 24* for approach to diagnosis and management of GABHS
  - gold standard for diagnosis is throat culture
  - rapid antigen detection testing: high specificity (95-99%), but moderate sensitivity (85%)
  - nucleic acid detection: high sensitivity (92%)
  - populations at increased risk of GABHS complications, such as Indigenous peoples in Canada, are more likely to benefit from testing
- suspected EBV (infectious mononucleosis)
  - peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or "monospot")

Management

- viral pharyngitis
  - antibiotics not indicated
  - symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants
- GABHS
  - antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and suppurative complications
  - 10 d of treatment required
  - incidence of glomerulonephritis is not decreased with antibiotic treatment
  - no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
  - routine F/U and/or post-treatment throat cultures are not required for most patients
  - F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier
- infectious mononucleosis (EBV)
  - self-limiting course; antibiotics are not indicated
  - symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
  - avoid heavy physical activity and contact sports for at least 1 mo or until splenomegaly resolves because of risk of splenic rupture
  - if acute airway obstruction, give corticosteroids and consult ENT

Palliative Care

Principles and Quality of Life

- early identification of patients who could benefit from a palliative approach to care
- support, educate, and treat both patient and family
- address physical, psychological, social, and spiritual needs
- establish a multidisciplinary team
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

End-of-Life Care Discussions

- see Palliative Medicine, PM6

Power of Attorney

- see Ethical, Legal, and Organizational Medicine, ELOM15

Instructional Advance Directives

- see Ethical, Legal, and Organizational Medicine, ELOM19

Symptom Management

- see Palliative Medicine, PM9

Complementary and Integrative Medicine

Prevalence and Use

- 50-75% of Canadians report some use of CAM over their lifetime, but only half will disclose this use to their physician
- use is highest in Western provinces and lowest in Atlantic provinces
- more likely to be used by younger patients and those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy, natural health products
- Indigenous peoples may receive support from a Traditional Healer in addition to receiving allopathic/colonial medical care
- try to be cautious about your own feelings about and experiences with different types of medicine; avoid dismissing or shaming

Natural Health Products (NHPs)

- over 50% of Canadians use NHPs
- most commonly used NHPs include: echinacea, ginseng, ginkgo, garlic, St. John's wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials (though many have been used for millennia)
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  - are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  - are you allergic to any plant products?
  - are you pregnant or breastfeeding?
- information resources: National Centre for CAM (https://www.nccih.nih.gov/), Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/regulation.html)

Serum Creatinine Does Not Reflect Creatinine Clearance in the Elderly

Instead, use:
CrCl = (weight in kg)(140 – age)(1.23)
(mL/min) (serum creatinine in µmol/L)

Multiply by 0.85 for females

Limitations:
Underestimates CrCl in patients without significant age-related decline in renal function
Overestimates CrCl in patients with muscle mass reduced beyond normal aging

Approach to Medication Review in the Elderly
Ask patient to bring all their current medications:
- Review Beers Criteria (2019) to identify potentially inappropriate medications
- Consider consulting https://deprescribing.org
- Screen for adverse drug effects and drug interactions
- Eliminate unnecessary medications (duplicate therapies or pharmacologic effects)
- Simplify dosing regimen where possible
- Discuss patient's goals of care to guide pharmacologic management of symptoms/disease
- Establish patient's understanding of medications and directions for use
- For tapering off sedatives, consider this tool: http://www.criugm.qc.ca/images/stories/les_chercheurs/risk_ct.pdf

Most Common Uses of CAM
- Back/neck problems
- Gynecological problems
- Anxiety
- Headaches
- Digestive problems
- Chronic fatigue syndromes

Table 25. Common Herbal Products

Common Name	Reported Uses	Possible Adverse Effects	Possible Drug Interactions
Black Cohosh	Menopausal symptoms, PMS, labour induction	Hepatitis, liver failure, GI discomfort, rashes	None reported
Chamomile	Mild sedative, anxiolytic, GI complaints, skin conditions (topical)	Allergic/contact dermatitis, anaphylaxis	Anxiolytics, sedatives, cyclosporine, warfarin
Echinacea	Common cold, flu, wound treatment, URTI, cancer	Hypersensitivity, GI discomfort, avoid use if immunosuppressed	None reported
Evening Primrose	PMS, breast pain, menopausal symptoms, eczema, RA	Headache, nausea, diarrhea, stomach upset, may increase risk of some pregnancy complications	Anticoagulants, antiplatelets
Feverfew	Migraine prevention, headache, RA, anti-inflammatory, fever, menstruation problems, psoriasis, allergies, asthma, tinnitus, dizziness, nausea, vomiting, intestinal parasites	Nausea, GI discomfort, irritation of mouth/skin, miscarriage (may affect uterine contractions), "post-fever few syndrome" (headaches, sleep disturbances, myalgias, arthralgias experienced after discontinuing feverfew)	Anticoagulants
Flaxseed Oil	Laxative, menopausal symptoms, source of omega-3 fatty acids, dietary supplement for DM, cholesterol, cancer	Diarrhea, raw/unripe flaxseeds may contain potentially toxic compounds, can worsen constipation if not taken with plenty of water	Do not take with other medications as fibre content can bind drugs
Garlic	Elevated lipids/cholesterol, atherosclerosis prevention, HTN, common cold, cancer prevention	Breath/body odour, GI irritation, contact dermatitis (raw garlic) May increase postoperative bleeding	Anticoagulants, saquinavir (HIV drug)
Ginger	Nausea, motion sickness, chemotherapy or pregnancy-induced nausea, RA, osteoarthritis	Heartburn, abdominal discomfort, diarrhea, gas, increased flow of bile (use with caution in gallstone disease), not to be used for morning sickness	Anticoagulants
Ginkgo Biloba	Increases peripheral circulation (Alzheimer's disease, dementia, intermittent claudication), eye problems, tinnitus, premenstrual syndrome, vertigo	Headache, stomach upset, bleeding, severe allergic reactions (whole plant/seeds/pulp), poisonous if ingested raw/roasted	Anticoagulants, ASA
Ginseng	Energy enhancer, decreases stress, adjunct support for chemotherapy/radiation	HTN, nervousness, insomnia, breakthrough bleeding, palpitations	Stimulant medications, antihypertensives, hormonal therapies
Glucosamine (Chondroitin)	Osteoarthritis	May cause kidney damage with long-term use, impaired glucose tolerance	Anticoagulants, caution if shellfish allergy
Saw Palmetto	BPH (adjunct to finasteride), chronic pelvic pain, decreased libido, migraine, hair loss	Mild GI distress, headache	None known
St. John's Wort	Mild to moderate depression, dietary supplement for menopausal symptoms, attention-deficit hyperactivity disorder, OCD, bladder problems, anxiety, sleep disorders, wound healing, dermatologic conditions (topical)	Photosensitivity, anxiety, dry mouth, GI symptoms, fatigue, sexual dysfunction, drowsiness, dizziness, headache, confusion	Antidepressants (SSRIs), OCPs, cyclosporine, digoxin, irinotecan (cancer medication), anticoagulants, contraindicated with indinavir
Valerian Root	Sedative, anxiolytic, depression, menopausal symptoms	Drowsiness, dizziness, headache, itching, digestive problems	CNS depressants, antihistamines, other sedatives

Zink T, Chaffin J. Herbal "health" products: What family physicians need to know. American Family Physician 1998;58:1133-1140; NIH National Centre for Complementary and Alternative Medicine website (http://nccam.nih.gov/)

Antimicrobial Quick Reference

Condition	Microorganisms	Antimicrobial
RESPIRATORY/ENT		
Acute Rhinitis (common cold)	Rhinovirus, coronavirus, influenza, RSV, parainfluenza, adenovirus	None
Pharyngitis (sore throat)	Rhinovirus, adenovirus, influenza, parainfluenza, coxsackie virus, coronavirus	None
Streptococcal Pharyngitis	Group A β-Hemolytic *Streptococcus*	**Children**: 1st line: If ≤27 kg, penicillin V 250 mg BID-TID x 10 d; if >27 kg: 500 mg BID-TID x 10 d use amoxicillin 50 mg/kg daily orally (maximum 1000 mg daily) x10 d. May be administered once daily or in 2 equally divided doses penicillin allergy (mild): cephalexin 40 mg/kg/d divided BID for 10 d (maximum 500 mg/dose) penicillin allergy (severe or anaphylaxis): Azithromycin 12 mg/kg/d (maximum 500 mg/dose) for 5 d **Adults**: 1st line: penicillin V 300 mg PO TID or 600 mg BID x 10 d penicillin allergy (mild): Cephalexin 500 mg PO BID x 10 d penicillin allergy (severe or anaphylactic): Azithromycin 12 mg/kg/d (maximum 500 mg/dose) x 5 d
Sinusitis	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *S. aureus*	**Children**: 1st line: amoxicillin/clavulanate 45 mg/kg/d divided BID (max 3 g/d) x 10 d 2nd line: amoxicillin/clavulanate 90 mg/kg/d divided BID (max 3 g/d) x 10 d penicillin allergy (mild): 3rd generation cephalosporin penicillin allergy (severe or anaphylactic): levofloxacin 10-20 mg/kg/d divided every 12 or 24 h **Adults**: 1st line: amoxicillin 500 mg PO TID x 5-10 d penicillin allergy: doxycycline 100 mg PO BID x 5-10d 2nd line or have risk factors for antibiotic resistance: amoxicillin/clavulanate 500 mg PO TID or 875 mg PO BID (7:1 formulation) x 5-10 d or respiratory fluoroquinolone such as levofloxacin 750 mg PO once daily or moxifloxacin 400 mg PO daily x5 d
Acute Otitis Media	*S. pneumoniae* *H. influenzae* *M. catarrhalis* Group A Strep *S. aureus*	**Children**: Treat with antibiotics if under age 6 mo If ages 6-24 mo, watchful waiting appropriate if parents can observe child for 48 h with plan to either reassess the child in 24-48 h; OR have the caregiver return if the child worsens anytime within 48 h OR provide an antimicrobial prescription to be filled if the child does not improve 10 d course if ages <24 mo, 5 d course if ages ≥24 mo 1st line: amoxicillin 75-90 mg/kg/d PO divided BID (max 3 g/d) penicillin allergy: cefuroxime acetil 30 mg/kg/d divided 2-3 times daily 2nd line: amoxicillin/clavulanate 45-60 mg/kg/d PO divided TID (7:1 formulation) x 10 d if under 35 kg amoxicillin/clavulanate 500 mg PO TID (7:1 formulation) x 10 d if over 35 kg Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops BID x 5 d **Adults**: 1st line: amoxicillin 500 mg PO TID x 7-10 d 2nd line: amoxicillin/clavulanate 500 mg PO TID or 875 mg PO BID x 7-10 d Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops BID x 5 d
Otitis Externa	*P. aeruginosa* Coliforms *S. aureus*	With or without tympanic membrane perforation: Ciprodex 4 drop BID x 7 d Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO BID x 4-8 wk
Bronchitis	*H. influenzae*, parainfluenza, coronavirus, rhinovirus, RSV	None
Community Acquired Pneumonia: Outpatient without Comorbidity	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae*	1st line: amoxicillin 1000 mg PO TID x 5-7 d (for patients over age 50 where mycoplasma infection is less likely) if atypical organisms present, add either of the following: clarithromycin 500 mg PO BID or 1000 mg (ER) PO once daily x 5-7 d azithromycin 500 mg PO on 1st d then 250 mg PO once daily x 4 d or 500 mg PO once daily x 3 d 2nd line: doxycycline 200 mg PO on 1st d then 100 mg PO BID x 5-7 d amoxicillin/clavulanate 875 mg PO BID x 5-7 d **PLUS** clarithromycin, azithromycin, or doxycycline as above if treatment failure: levofloxacin 500-750 mg PO once daily x 5 d OR moxifloxacin 400 mg PO once daily x 5 d
Community Acquired Pneumonia: Outpatient with Comorbidity	S. pneumoniae M. pneumoniae C. pneumoniae H. influenzae	
Dental Infections/Periapical and Periodontal Abscesses	Oral Flora	penicillin V potassium 500 mg PO QID x 7-10 d clindamycin 300 mg PO QID or 600 mg BID x 7-10 d
GASTROENTEROLOGY		
Diarrhea – Enteritis	*Enterotoxigenic E. coli* *Campylobacter* *Salmonella* *Shigella* Viruses Protozoa	azithromycin is the preferred agent given growing resistance to quinolones, particularly in Southeast Asia azithromycin 1000 mg PO single dose or 500 mg PO once daily x 1-3 d (children: 10 mg/kg/d x 3 d) ciprofloxacin 750 mg PO single dose or 500 mg PO BID x 1-3 d (prevention: 500 mg PO once daily) levofloxacin 500 mg PO once daily x 1-3 d (prevention: 500 mg PO once daily)
Diarrhea – Post Antibiotics (common with clindamycin)	*C. difficile*	Mild to moderate (WBC <15 x 10^9 /L and Cr <1.5 x baseline): vancomycin 125 mg PO QID x 10-14 d (children: vancomycin 40 mg/kg daily divided in 4 doses) Severe (WBC ≥15 x 109/L and Cr ≥1.5 x baseline): vancomycin 125 mg PO QID x 10-14 d (children: vancomycin 40 mg/kg/d PO divided TID-QID x 10-14 d max 500 mg/d)
Peptic Ulcer Disease (non-NSAID related)	*H. pylori*	PPI PO BID + amoxicillin 1000 mg PO BID + clarithromycin 500 mg PO BID + metronidazole 500 mg PO BID x 7 d OR PPI PO BID + bismuth subsalicylate 525 mg PO QID + metronidazole 500 mg PO QID + tetracycline 500 mg PO QID x 7-14 d PPI: lansoprazole 30 mg or omeprazole 20 mg or pantoprazole 40 mg or rabeprazole 20 mg

Condition	Microorganisms	Antimicrobial
DERMATOLOGIC		
Head and Pubic Lice (crabs)	*Pediculus humanus capitis* *Phthirus pubis*	permethrin cream 1%: apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk
Vulvovaginal Candidiasis	*Candida*	Treat only if patient is symptomatic fluconazole 150 mg PO x 1 dose miconazole 2% cream (Monistat 7®): one applicator (5 g) intravaginally QHS x 7 d Multiple other OTC azole treatments
Bacterial Vaginosis	Overgrowth of: *G. vaginalis* *M. hominis* Anaerobes	If patient is asymptomatic, treatment is unnecessary unless high-risk pregnancy, prior IUD insertion, gynaecologic surgery, induced abortion, or upper tract instrumentation 1st line: metronidazole 500 mg PO BID x 7 d metronidazole 0.75% gel: one applicator (5 g) intravaginally QHS x 5 d clindamycin 2% cream: one applicator (5 g) intravaginally QHS x 7 d 2nd line: metronidazole 2 g PO x 1 dose clindamycin 300 mg PO BID x 7 d
Herpes	Herpes simplex virus	1° episode: acyclovir 400 mg PO TID x 5-10 d OR famciclovir 250 mg PO TID x 5 d OR valacyclovir 1000 mg PO BID x 10 d Recurrent Episode: acyclovir 800 mg PO TID x 2 d or 800 mg PO BID x 5 d famciclovir 1000 mg PO BID x 1 d or 125 mg PO BID x 5d or 500 mg PO once followed by 250 mg PO BID x 2 d valacyclovir 500 mg PO BID x 3 d or 1000 mg PO once daily x 5 d Pregnancy: 1° episode: acyclovir 400 mg PO TID TID x 7-10 d OR valacyclovir 1 g PO BID x 7-10 d Prior infection within previous yr: acyclovir 800 mg PO BID x 5 d or 800 mg PO TID x 2 or valacyclovir 500 mg PO BID x 3 d or 1g PO OD x 5 d daily suppressive therapy: acyclovir 400 mg PO TID daily or valacyclovir 500 mg PO BID at 36 wk
Gonorrhea/Chlamydia	*N. gonorrhoeae* *C. trachomatis*	ceftriaxone 250 mg IM x 1 dose + azithromycin 1 g PO x 1 dose OR doxycycline 100 mg PO BID x 7 d No intercourse for one week after treatment
Mastitis	*S. aureus* *S. pyogenes*	cloxacillin 500 mg PO QID x 7 d cephalexin 500 mg PO QID x 7 d
Tinea Cruris/Pedis (jock itch/ athlete's foot)	*Trichophyton*	clotrimazole 1% cream BID ketoconazole 2% cream BID
Uncomplicated Cellulitis	*S. aureus* Group A Strep.	**Children:** 1st line: cephalexin 50-100 mg/kg/d divided QID x 10-14 d 2nd line: cloxacillin 50 mg/kg/d divided QID x 10-14 d clindamycin 25 mg/kg/d x 10-14 d **Adults:** 1st line: cephalexin 500 mg PO QID x 10-14 d 2nd line: cloxacillin 500 mg PO QID x 10-14 d clindamycin 300 mg PO x 10-14 d

Landmark Family Medicine Trials

Trial Name	Reference	Clinical Trial Details
HYPERTENSION		
DASH	N Engl J Med 1997; 336:1117-1124	**Title:** A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure **Purpose**: To assess the impacts of dietary modifications on blood pressure patterns. **Methods**: RCT involving 459 patients randomized to receive a control diet, a diet rich in fruits and vegetables, or a combination diet rich in fruits, vegetables and low-fat dairy products. **Results**: The combination diet exhibited the most promising results. In normotensive patients the combination diet reduced systolic and diastolic pressure by 5.5 and 3.0 mmHg more than the control diet, respectively. Amongst patients with hypertension the combination diet reduced systolic and diastolic blood pressure by 11.4 and 5.5 mmHg, respectively. **Conclusion**: The combination diet exhibited promising results for the reduction of blood pressure.
Systolic blood pressure intervention trial (SPRINT)	N Engl J Med 2015; 373:2103-2116	**Title**: Intensive vs. Standard Blood Pressure Control **Purpose**: To assess the effectiveness of various targets for systolic BP with regard to lowering CV mortality **Methods:** RCT including 9361 patients with a systolic BP >130 mmHg and high risk for CV events. Patients were randomized to a target BP of 120 mmHg (standard target) or 140mmHg (intensive target). The outcomes of interest were MI, acute coronary syndromes, stroke, HF, or death. **Results:** After 3 yr of follow up the prevalence of cardiovascular complications were significantly reduced within the intensive treatment group when compared to the standard treatment group - 1.65%/yr and 2.19%/yr, respectively. **Conclusion**: With regard to patients who are at high risk for CV events, intensive treatment of their BP resulted in decreased incidence of major CV complications.
Heart outcomes prevention evaluation-3 (HOPE-3)	N Engl J Med 2016; 374:2021-2031	**Title:** Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease **Purpose**: To assess the benefits of statins in intermediate-risk populations without CV disease. **Methods**: RCT consisting of 12705 patients who did not presently have CV disease but were deemed to be at intermediate risk. Patients were randomized to receive either 10mg of rosuvastatin per day or a placebo. The outcome of interest were death by CV cause, non-fatal MI, or non-fatal stroke. **Results**: LDL levels were reduced by 26.5% within the treatment group in comparison to those that received the placebo. The prevalence of vascular events was significantly reduced within the rosuvastatin group (3.7%) when compared to the placebo group (4.8%). **Conclusion**: The use of rosuvastatin in an intermediate-risk group without CV disease reduced the prevalence of vascular events when compared to those that did not receive treatment.

Trial Name	Reference	Clinical Trial Details
Chronic hypertension and pregnancy (CHAP)	N Engl J Med. 2022;386(19):1781	**Title**: Treatment for Mild Chronic Hypertension during Pregnancy **Purpose**: Historically, only severe HTN (BP ≥160/110 mmHg) was treated. This study aims to assess the benefits of treating mild chronic non-severe HTN (BP ≥140/90 mmHg). **Methods**: RCT consisting of 2408 pregnant women with mild chronic HTN and singleton fetuses at a gestational age of less than 23 wk. Patients were randomized to receive the standard medication for severe HTN in pregnant women or no treatment at all. Primary outcomes were preeclampsia, medically indicated preterm birth (<35 wk gestation), placental abruption, or fetal/neonatal death. **Results**: The incidence of the primary outcome was substantially lower within the treatment group as opposed to the control group - 30.2% and 37.0%, respectively. **Conclusion**: Targeting a BP below 140/90 mmHg using anti-HTN medications resulted in improved health and pregnancy outcomes.
MENOPAUSE/HORMONE REPLACEMENT THERAPY		
Women's Health Initiative Trial	JAMA 2002;288:321-333	**Title**: Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women **Purpose**: To assess the impacts of combined hormone therapy in healthy post-menopausal women. **Methods**: RCT consisting of 16608 postmenopausal women with an intact uterus. Participants were randomized to combined estrogen and progesterone, or a placebo. The outcomes of interest were coronary heart disease (CHD) and breast cancer. **Results**: Amongst the treatment group there were 286 cases of CHD, and 290 cases of breast cancer. **Conclusion**: Results show that the overall health risks exceed the benefits of the combined hormone therapy.
HEART FAILURE		
IRONMAN	Lancet 2022;400:2199-2209	**Title**: Intravenous Ferric Derisomaltose in Patients with Heart Failure and Iron Deficiency **Purpose**: To determine the effects of IV ferric derisomaltose on CV events in patients with HF. **Methods**: RCT of 1137 patients with HF (Left ventricular ejection fraction ≤ 45%) and transferrin saturation <20% or serum ferritin <10µg/L who were randomly assigned to receive ferric derisomaltose or standard of care. Primary outcomes were recurrent hospital admissions for HF and CV-related death. **Results**: The ferric derisomaltose-treated group had 336 primary endpoints (22.4 per 100 patient-years) whereas the standard of care group had 411 (27.5 per 100 patient-years) (RR 0.82; 95%CI, 0.66 to 1.02). Fewer serious cardiac adverse events were seen in the ferric derisomaltose group as compared to controls (difference -7.00%; 95% CI, -12.69 to -1.32; p=0.016). **Conclusion**: Ferric derisomaltose is beneficial in patients with HF with reduced ejection fraction and iron deficiency as it is associated with reduced hospital admissions for HF and CV death.

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G Gastroenterology

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Acronyms

ALF	acute liver failure
BE	Barrett's esophagus
BT	biologic therapy
CCK	cholecystokinin
CD	Crohn's disease
CMV	cytomegalovirus
CNS	central nervous system
DGP	deamidated gliadin peptides
DES	diffuse esophageal spasm
EBV	Epstein-Barr virus
EGD	esophagogastroduodenoscopy
EIM	extraintestinal manifestation
EN	enteral nutrition
EPEC	enteropathogenic E. coli
ERCP	endoscopic retrograde cholangiopancreatography
ETEC	enterotoxigenic E. coli
EUS	endoscopic ultrasound
EVL	endoscopic variceal ligation
GE	gastroesophageal
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HRS	hepatorenal syndrome
HSV	herpes simplex virus
HUS	hemolytic uremic syndrome
HVPG	hepatic venous pressure gradient
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICP	intracranial pressure
INH	isoniazid
LES	lower esophageal sphincter
LGIB	lower gastrointestinal bleed
MRCP	magnetic resonance cholangiopancreatography
MS	multiple sclerosis
NAC	N-acetylcysteine
NAFLD	non-alcoholic fatty liver disease
NERD	non-erosive reflux disease
NMS	neuroleptic malignant syndrome
O&P	ova and parasites
PBC	primary biliary cirrhosis
PN	parenteral nutrition
PSC	primary sclerosing cholangitis
PTC	percutaneous transhepatic cholangiography
PUD	peptic ulcer disease
RA	rheumatoid arthritis
RLQ	right lower quadrant
RUQ	right upper quadrant
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt
TNF	tumour necrosis factor
TPN	total parenteral nutrition
TTG	tissue transglutaminase
UC	ulcerative colitis
UGIB	upper gastrointestinal bleed

Anatomy Review

Overview of Gastrointestinal Tract

- the GI tract runs from mouth to anus ("gum to bum")

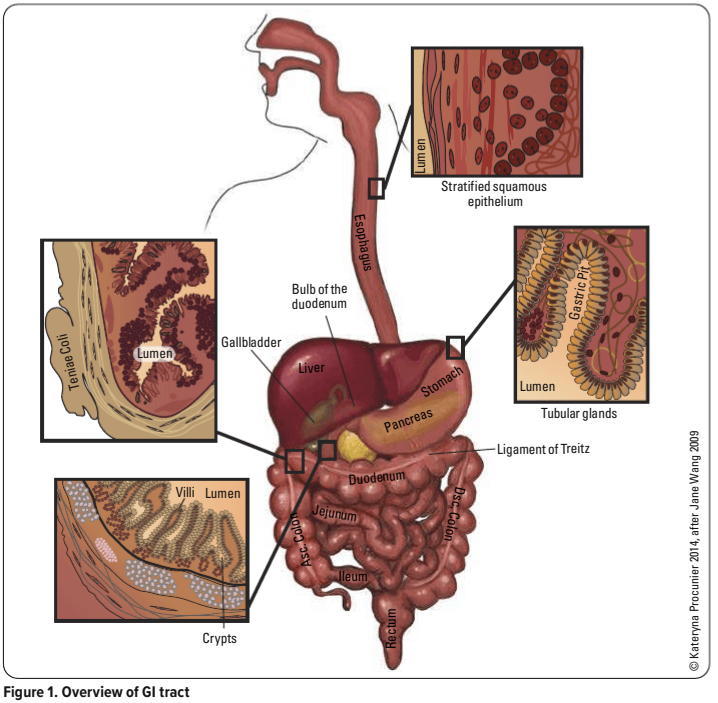


Figure 1. Overview of GI tract

Table 1. Summary of GI Tract Structure and Function

Organ	Function	Blood Supply	Innervation	Histology and Structural Features
Esophagus	Muscular tube approximately 40 cm long with a diameter of 2 cm Extends from the pharynx to the stomach	Arterial: left gastric artery and left inferior phrenic artery Venous: Left gastric vein ➔ portal venous system Esophageal veins ➔ azygos vein ➔ inferior vena cava (systemic)	Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks) Sympathetic innervation via thoracic trunks of the greater splanchnic nerves	Mucosa: stratified squamous epithelium Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells Muscularis propria (muscularis externa): inner circular, outer longitudinal muscle Upper 1/3: striated muscle Middle 1/3: transition zone Lower 1/3: smooth muscle
Stomach	Prepares and delivers food to intestine for digestion and absorption Secretes acid to reduce enteric infections/pneumonia and facilitate digestion of protein and absorption of iron/B_{12} Secretes intrinsic factor (IF) to facilitate B_{12} absorption Minor contribution to initial protein digestion via pepsin	Lesser curvature Right and left gastric arteries (from celiac trunk) Greater curvature Right and left gastro-omental (gastroepiploic) arteries (from gastroduodenal and splenic arteries respectively) Fundus: short and posterior gastric arteries (from the splenic artery)	Parasympathetic innervation via vagus nerve Sympathetic innervation via celiac plexus (from T6-T9)	5 parts Cardia Fundus Body Antrum Pylorus
Duodenum	Modulates enteral pH via secretin ➔ decreased gastric acid secretion, increased bicarbonate secretion Secretes CCK to stimulate gallbladder contraction Site of iron absorption	Branches of celiac artery and superior mesenteric artery	Parasympathetic innervation via vagus nerve Sympathetic innervation via greater and lesser splanchnic nerves	4 parts Superior (5 cm) Descending (7-10 cm) Horizontal (6-8 cm) Ascending (5 cm) 1st part is intraperitoneal; rest is retroperitoneal
Jejunum	Absorption of sodium, water, and nutrients (protein, carbohydrates, fat, folic acid, and vitamin A, B, C, D, E, K)	Superior mesenteric artery	Parasympathetic innervation via fibres of the posterior vagal trunk Sympathetic innervation via fibres of T8-T10	Deep red colour 2-4 cm in thickness Thick and heavy wall Plicae circulares are large, tall, and closely packed Has long vasa recta Scant fat in mesentery Scant Peyer's patches
Ileum	Absorption of sodium, water, nutrients, soluble vitamins (only site of vitamin B_{12} absorption), and bile salts (entero-hepatic circulation)	Superior mesenteric artery	Same as jejunum	In comparison to jejunum: Paler pink colour 2-3 cm in thickness Thin and light walls Plicae circulares are small and sparse Contains more mesenteric fat Many Peyer's patches
Large Bowel	Absorption of water (5-10% of total water) Bacteria: provide further digestion of chyme and metabolism of undigested carbohydrate to short chain fatty acids Formation and storage of feces	Branches of superior and inferior mesenteric arteries Rectal blood supply: sigmoid, right pudendal, and rectal arteries	Parasympathetic innervation via vagus nerve Sympathetic innervation via greater and lesser splanchnic nerves	Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal Features include teniae coli, haustra, and omental appendices
Liver	Glucose homeostasis Plasma protein synthesis Lipid and lipoprotein synthesis Bile acid synthesis and secretion Vitamin A, D, E, K, B12 storage Biotransformation, detoxification Excretion of compounds Immune surveillance	2 sources Portal vein (75-80%) Hepatic artery (20-25%)	Parasympathetic innervation via fibres of the anterior and posterior vagal trunks Sympathetic innervation via fibres of the celiac plexus	Largest internal organ Composed of 4 lobes (left, right, caudate, quadrate), and divided into 8 segments
Biliary Tract	Gallbladder stores and releases bile that is produced in the liver Bile emulsifies fat and is composed of cholesterol, lecithin, bile acids, and bilirubin CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release	Cystic artery	Parasympathetic innervation via vagus nerve Sympathetic and visceral innervation via celiac nerve plexus Somatic afferent fibres via right phrenic nerve	Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct, and ampulla of Vater
Pancreas	Endocrine function: islets of Langerhans produce glucagon, insulin, and somatostatin (from the α, β, and δ cells, respectively) Exocrine function: digestive enzymes, including amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase, are produced	Anterior superior pancreaticoduodenal artery (from the celiac trunk) Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery) Dorsal pancreatic artery (from the splenic artery) Pancreatic veins drain into the portal, splenic, and superior mesenteric veins	Parasympathetic innervation via vagus nerve Sympathetic innervation via abdominopelvic splanchnic nerves	4 parts of pancreas: head (includes uncinate process), neck, body, and tail (Major) pancreatic duct connecting to common bile duct prior to ampulla of Vater Accessory pancreatic duct connected directly to duodenum

Visualizing the Gastrointestinal Tract

- see Medical Imaging, MI11

Esophagus, Stomach, Duodenum

- EGD: best visualization of mucosa; also allows for therapeutic intervention (e.g. banding varices, thermal therapy/clipping/injecting bleeding ulcers, and dilatation for the treatment of esophageal strictures)
  - consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation), possibility of fistulae
  - endotracheal intubation first if massive UGIB, acidemia, or inability to protect airway

Small Bowel

- most difficult to visualize, especially if mucosal detail is needed
- CT enterography favoured over small bowel follow-through in view of accuracy, but both have low sensitivity
- MRI small bowel imaging increasingly available, especially useful if radiation exposure is an issue (e.g. young patient, multiple radiological images already done)
  - note: MRI enteroclysis, luminal contrast is administered by nasojejunal (NJ) tube to dilate the small bowel – disliked by both radiologist and patient, but may improve sensitivity
- "double balloon" enteroscopy (enteroscope with proximal and distal balloons to propel endoscope into jejunum from mouth or into jejunum/ileum from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction, known strictures) is also accurate in diagnosis but does not provide any therapeutic intervention

Colon and Terminal Ileum

- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis, and severe colitis (increased risk of perforation)
- CT colonography ("virtual colonoscopy") more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), and fistulae; increasing evidence for use in colorectal cancer screening, especially for assessment of right side of colon in cases where colonoscopy is less sensitive
  - most often used when optical endoscopic colonoscopy is risky (e.g. frail elderly) or unsuccessful (e.g. stricture)

Pancreatic/Biliary Duct

- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if therapeutic intervention likely to be required (strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required)
- EUS can provide detailed anatomy of biliary tree and pancreas with potential for sampling/intervention (e.g. cyst drainage)

Acute Upper Abdominal Pain
Remember to rule out thoracic sources (e.g. MI, pneumonia, dissecting aneurysm)

Differential Diagnosis of Common Complaints

- see General Surgery and Thoracic Surgery, GS4

Table 2. Differential Diagnosis of Common Presenting Complaints

CHRONIC/ RECURRENT ABDOMINAL PAIN	Inflammatory	Neoplastic/ Vascular	Toxin	Other
	PUD Biliary colic IBD Chronic pancreatitis	Gastric cancer Recurrent bowel obstruction Mesenteric ischemia Sickle cell anemia	Lead poisoning	Mittelschmerz Endometriosis Porphyria IBS Radiculopathy Diverticular disease Anterior cutaneous nerve entrapment syndrome

ACUTE DIARRHEA	Inflammatory		Non-Inflammatory	
*Causes of bloody diarrhea	**Bacterial** *Shigella** *Salmonella** *Campylobacter** *Yersinia** *E. coli* (EHEC 0157:H7)*	**Protozoal** *E. histolytica** (amoebiasis) *Strongyloides* **Others** NSAIDs IBD* Ischemia*	**Bacterial** *S. aureus* *C. perfringens* *B. cereus* *E. coli* (enterotoxigenic, enteropathogenic) *Salmonella enteritidis* *Vibrio cholera* **Protozoal** *Giardia lamblia*	**Viral** Rotavirus Norwalk CMV **Drugs** ABx Colchicine Laxatives Antacids (magnesium)

Obscure but Treatable Causes of Abdominal Pain
Acute Intermittent Porphyria
Hereditary Angioedema
Familial Mediterranean Fever
Vasculitis (e.g. polyarteritis nodosa)

Inflammatory Diarrhea: Occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids. Diarrhea may be profuse or very small in volume. Often associated with abdominal pain ± fever and chills. Stool may be positive for white blood cells

Non-Inflammatory Diarrhea: No damage to the mucosal lining. Nausea/vomiting may be present. Fever, chills, blood in the stool, severe abdominal pain, or tenderness are not present. Stool is negative for white blood cells

Table 2. Differential Diagnosis of Common Presenting Complaints

CHRONIC DIARRHEA	**Organic**				**Gastric cancer**
*Causes of bloody diarrhea	**Inflammatory**	**Secretory**	**Steatorrhea**	**Osmotic**	
	IBD* Infectious (TB, CMV, HSV) Ischemic bowel* Radiation colitis Neoplasia *C. difficile* rarely causes bleeding	Stimulant laxatives Post-ileal resection/ cholecystectomy (bile salts) Bacterial toxins Vasculitis Neoplasia* (colon cancer, carcinoid, vasoactive intestinal peptide tumour (i.e. VIPoma)) Addison's disease Congenital syndromes	*Giardia lamblia* Celiac disease Chronic pancreatitis Chronic cholestasis Bacterial overgrowth	Osmotic laxatives Lactose intolerance Chewing gum (sorbitol, mannitol)	IBS Constipation (overflow diarrhea) Anal sphincter dysfunction
CONSTIPATION: if no associated rectal bleeding/weight loss, etc., usually no cause found (and dysmotility assumed)					
	Colorectal cancer Stricture Extrinsic compression Anal disease Rectocele	Medications (narcotics, antidepressants, calcium channel blockers) Metabolic (DM, thyroid, hypercalcemia)	Neurologic (Parkinson's, MS, stroke) Collagen vascular disease (scleroderma, dermatomyositis)		
NAUSEA/VOMITING	**With Abdominal Pain**		**Without Abdominal Pain**		
	Relieved by Vomiting	**Not Relieved by Vomiting**	**Headache/Dizziness**		**No Other Symptoms**
	Gastric outlet obstruction Small bowel obstruction GERD (regurgitation more common)	Gallbladder disease Pancreatitis MI Hepatitis Infectious Gastroenteritis	Cerebral tumour Migraine Vestibular disease Increased ICP		Drugs Uremia Pregnancy Metabolic (e.g. hypercalcemia) Gastroparesis (e.g. DM) Ketoacidosis
DYSPEPSIA	**Common**		**Uncommon**		**Rare**
	Functional dyspepsia Drug side effect Peptic ulcer GERD (esophagitis)		Angina CD Cancer (stomach, pancreas, liver) Gallstones Aerophagia		***Giardia lamblia*** Malabsorption (celiac sprue) Pancreatitis
UPPER GI BLEED	**Common**		**Uncommon**		**Rare**
	Ulcers (*H. pylori*, ASA, NSAIDs) Esophageal varices Mallory-Weiss tears Erosive esophagitis Erosive gastritis		Tumours Arteriovenous malformation Dieulafoy's lesion (arterial) Gastric antral vascular ectasia (GAVE) Portal hypertensive gastropathy		Aorto-enteric fistulae Hemobilia
LOWER GI BLEED	**Common**		**Uncommon**		**Rare**
	Diverticulosis Ischemia Angiodysplasia (elderly) Infectious Anorectal (hemorrhoids, fissure, ulcer)		UGIB (brisk) Post-polypectomy Radiation colitis IBD		Intussusception Vasculitides Stercoral ulcer Coagulopathies
DYSPHAGIA	**Mechanical (Solids)**		**Motility (Solids and Liquids)**		**Other**
	Peptic stricture/cancer Eosinophilic esophagitis Extrinsic compression Schatzki ring/esophageal web Zenker's diverticulum		Achalasia DES Scleroderma		Foreign body Eosinophilic esophagitis
ODYNOPHAGIA	**Infection**	**Inflammation/Ulceration**	**Drugs**		**Other**
	Candida HSV CMV (common in those who are immunosuppressed)	Caustic damage Eosinophilic esophagitis	Quinidine Iron Vitamin C ABx (e.g. tetracycline) Bisphosphonates		Radiation
ABDOMINAL DISTENSION	**Fluid (Ascites)**	**Flatulence**	**Feces**		**Other**
	Portal HTN / **Normal Portal Pressure**				
	Cirrhosis Cardiac failure Hepatic vein thrombosis / Cancer (especially ovarian) Pancreatitis TB	Functional bowel disease (e.g. IBS) Fibre Lactose intolerance Chewing gum (e.g. sorbitol, mannitol)	Constipation Colonic obstruction Dysmotility		Pregnancy (fetus) Pregnancy (fetus) Obesity (fat) Blood Large tumours (fatal growth) Organomegaly

IBD is a common cause of bloody diarrhea but can be diagnosed only if mimickers are excluded; such as infection, ischemia, and medication induced

Commonly Forgotten Causes of Vomiting
Drugs
Uremia
CNS disease
Pregnancy
- Cannabis (cannabinoid hyperemesis)

Differentiating Between Dysphagia and Odynophagia
Dysphagia: Difficulty swallowing due to mechanical obstruction or dysmotility of the esophagus or pharynx
Odynophagia: Pain when swallowing due to ulceration or inflammation (e.g. candida esophagitis) in the esophagus or pharynx

Differential Diagnosis of Abdominal Distension

6 Fs
Fat
Feces
Fetus
Flatus
Fluid
Fatal growth

Table 2. Differential Diagnosis of Common Presenting Complaints

JAUNDICE (UNCONJUGATED BILIRUBIN)	**Overproduction**	**Decreased Hepatic Intake**	**Decreased Conjugation**
	Hemolysis Ineffective erythropoiesis (e.g. megaloblastic anemias)	Gilbert's syndrome Drugs (e.g. rifampin)	Drug inhibition (e.g. chloramphenicol) Crigler-Najjar syndromes type I and II Gilbert's syndrome Neonatal jaundice
JAUNDICE (CONJUGATED BILIRUBIN)	**Hepatocellular Disease**		**Biliary Obstruction**
	Drugs Cirrhosis (any cause) Inflammation (hepatitis, any cause) Infiltrative (e.g. hemochromatosis) Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy) PBC PSC Sepsis Postoperative/TPN		Intraductal obstruction: Gallstones Biliary stricture Parasites Malignancy (cholangiocarcinoma) Sclerosing cholangitis Extraductal obstruction: Malignancy (e.g. pancreatic cancer, lymphoma) Metastases in periportal nodes Inflammation (e.g. pancreatitis)

Esophagus

Gastroesophageal Reflux Disease

Definition

- a condition which develops when the reflux of gastric content causes troublesome symptoms or complications

Etiology

- increased number of transient relaxations of the LES – most common cause
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, obesity, pregnancy, acid hypersecretion (rare) from Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see General Surgery and Thoracic Surgery, GS23)

Clinical Features

- "heartburn" (pyrosis) and regurgitation (together are 80% sensitive and specific for reflux); less sensitive and less specific: water brash, sensation of a lump in the throat (globus sensation), and frequent belching
- non-esophageal symptoms are increasingly recognized as being poor predictors of reflux

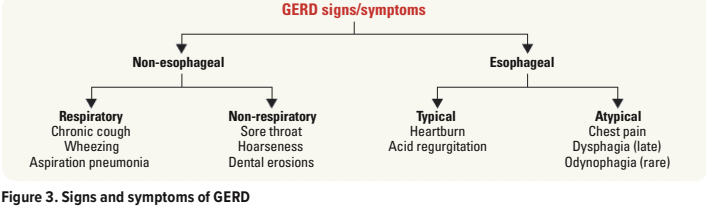


Figure 3. Signs and symptoms of GERD

Investigations

- usually, a clinical diagnosis is sufficient based on symptom history and relief following a trial of pharmacotherapy (PPI: symptom relief 80% sensitive for reflux)
- however, response to anti-secretory agents such as PPI is not a requirement for GERD diagnosis
- gastroscopy indications
  - absolute indications
    - heartburn accompanied by red-flags (bleeding, weight loss, dysphagia, persistent vomiting, family history of GI cancer, etc.)
    - persistent reflux symptoms or prior severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI BID
    - history suggests esophageal stricture especially dysphagia
    - high-risk for BE (male, ages >50, obese, white, tobacco use, long history of symptoms)
- repeat endoscopy after 8 wk of PPI therapy/ indicated if severe esophagitis because it can mask BE or symptoms

Ischemic Colitis
The splenic flexure and rectosigmoid junction are watershed areas and are susceptible to ischemia. History and symptoms include acute onset crampy left abdominal pain, rectal bleeding, in addition to possible abdominal tenderness on exam. Risk factors include atherosclerotic risk factors, vasoconstricting medications, and history of low flow state

Dyspepsia = postprandial fullness, early satiety, epigastric pain or burning

Foods/Substances that May Aggravate GERD Symptoms (but diet does not change the underlying disease)

- EtOH
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices

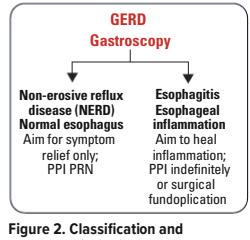


Figure 2. Classification and gastroscopic findings of GERD

Side Effects of Long-Term Use of PPIs

Only some (*C. difficile* diarrhea, hypomagnesemia, vitamin B^{12} deficiency, small bowel bacterial overgrowth) seem to be related to suppressing gastric acid whereas others (pneumonia, fractures, chronic kidney disease, dementia) have no apparent pathophysiological relationship

Stopping PPIs can increase gastric acid above baseline by a "rebound effect" causing heartburn even in healthy volunteers

May increase the risk of IBD with prolonged regular use

These associations do not preclude long term use of PPIs in patients with esophagitis or peptic ulcer, or those needing gastric protection when taking NSAIDs or anti-platelet drugs, but do emphasize the importance of being as definitive as possible when making these diagnoses and accurately assessing risk-benefit ratios (as is true for all drugs)

- esophageal manometry (study of esophageal motility): indicated in patients who have non-cardiac chest pain and/or dysphagia with normal gastroscopy
  - done to diagnose abnormalities of peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure intact esophageal function; exclude alternative diagnoses like scleroderma and achalasia
  - surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to alleviate symptoms if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- 24 h pH monitoring: most accurate test for reflux, but not required or performed in most cases
  - most useful if PPIs do not improve symptoms

Up to 25% of patients with BE do not report symptoms of GERD

Treatment
- PPIs are the most effective therapy and usually need to be continued as maintenance therapy
- empiric 8 wk trial of PPI in patients with classic GERD symptoms; PPIs are the most effective therapy; may need to be continued as maintenance therapy
- discontinuation of PPIs after 8 wk in recovered patients without Barrett's esophagus or erosive esophagitis; symptoms may recur if therapy is discontinued
- on-demand: antacids ($Mg(OH)_2$, $Al(OH)_3$), alginate, H_2-blockers, or PPIs can be used for non-erosive esophagitis (NERD)
- diet helps symptoms, not the disease; avoid EtOH, coffee, spices, tomatoes, and citrus juices
- only beneficial lifestyle changes are weight loss (if obese or significant weight gain) and elevating the head of bed (if nocturnal symptoms)
- symptoms may recur if therapy is discontinued

Complications
- esophageal stricture disease – scarring can lead to dysphagia (solids)
- esophagitis (e.g. ulceration, bleeding)
- BE and esophageal adenocarcinoma – EGD is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

Screening for Esophageal Adenocarcinoma in Patients with Chronic Gastroesophageal Reflux Disease
CMAJ 2020;192(27):E768-E777
Though Barrett's esophagus increases the incidence of esophageal adenocarcinoma, the Canadian Task Force on Preventive Health Care currently does not recommend routine screening for esophageal adenocarcinoma and precursor conditions, including Barrett's esophagus, in adults with chronic GERD without red flag features (e.g. dysphagia, odynophagia, weight loss, anemia, gastrointestinal bleeding). In this systematic review, no clinically significant survival benefits were identified in patients undergoing screening. This systematic review reported that patients receiving screening may be unnecessarily exposed to harm, ranging from pre-procedural anxiety to endoscopic injury. Strikingly, the presence of risk factors for esophageal adenocarcinoma, including age, male sex, and family history, is not sufficient to warrant screening endoscopy in patients with chronic GERD. On the other hand, patients with known Barrett's esophagus should be referred to a Gastroenterologist for endoscopy.

Barrett's Esophagus

Definition
- metaplasia of normal squamous esophageal epithelium to intestinal columnar epithelium

Etiology
- thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Clinical Features
- prominent GERD symptoms

Epidemiology
- in North America and Western Europe, 0.5-20% of adults are thought to have BE
- up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- more common in males, ages >50, White individuals, smokers, overweight, hiatus hernia, and long history of reflux symptoms

Clinical Guidelines Update on the Diagnosis and Management of Barrett's Esophagus
For a report reviewing the US and international guidelines on the diagnosis and management of BE, please refer to: Dig Dis Sci 2018;63:2122-2128

Pathophysiology
- endoscopy shows salmon pink mucosa in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes the esophageal lining to premalignant changes characterized as low or high-grade dysplasia, which then progresses to adenocarcinoma

Significance
- rate of malignant transformation is approximately 0.12% per yr for all BE patients prior to dysplasia
- risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance

Treatment
- acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication) may reduce the transformation of BE to dysplasia
- surveillance gastroscopy every 3-5 yr if no dysplasia
- high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes
  - however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation
- if low grade dysplasia, both surveillance (every 6 mo for 1 yr then annually) and endoscopic ablation/resection are satisfactory options

Randomized Trial of Medical vs. Surgical Treatment for Refractory Heartburn
NEJM 2019;381:1513-1523
Patients with PPI-refractory and reflux-related heartburn (n=78) were randomly assigned to surgical treatment (laparoscopic Nissen fundoplication), active medical treatment (omeprazole plus baclofen, and desipramine prn), or control medical treatment (omeprazole plus placebo). The incidence of treatment success in the surgical treatment group (67%) was significantly greater than that in the active medical treatment group (28%; P=0.007) or control medical treatment group (12%; P<0.001).

Dysphagia

Definition
- difficulty swallowing

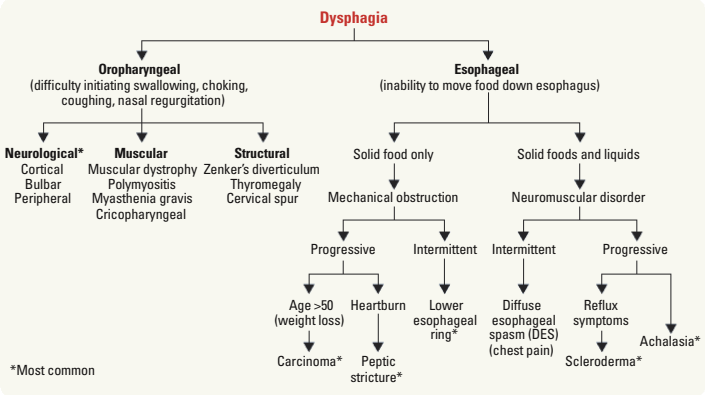


Figure 4. Approach to dysphagia (eosinophilic esophagitis omitted)

Remember:
Dysphagia = Difficulty in swallowing
Odynophagia = Pain on swallowing

Key Questions in Dysphagia

Abnormal features when initiating the act of swallowing?

Associated symptoms? (regurgitation, chest pain, change in voice pitch, weight loss)

Solids, liquids, or both?

Intermittent or progressive?

History of heartburn?

Change in eating habits/diet?

Esophageal Motor Disorders

Clinical Features
- dysphagia with solids and liquids
- chest pain (in some disorders)

Diagnosis
- motility study (esophageal manometry)
- barium swallow sometimes helpful

Causes
- idiopathic
- achalasia
- scleroderma
- DM
- DES: rare and can be difficult to diagnose due to intermittent presentation

Table 3. Esophageal Motor Disorders

Disorder	Achalasia	Scleroderma	Diffuse Esophageal Spasm
Definition	Failure of smooth muscle relaxation at LES Increased LES pressure Progressive loss of peristaltic function	See Rheumatology, RH14 Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening)	Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)
Etiology	Usually idiopathic Secondary or pseudo-achalasia e.g. malignancy, Chagas disease (Trypanosoma cruzi)	Involves autoimmune, genetic, hormonal, and environmental factors Dysphagia: caused by reflux, dysmotility, or both	Idiopathic
Pathophysiology	Inflammatory degeneration of Auerbach's plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis	Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia	Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis
Diagnosis	CXR: no air in stomach, dilated esophagus Barium studies: esophagus terminates in narrowing at LES ("bird's beak") Endoscopy: normal mucosa Manometry: definitive diagnosis (signs listed above)	Clinical features of scleroderma Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus	Barium x-ray: "Corkscrew pattern" Manometry: >20% premature contractions Endoscopy: normal mucosa
Treatment	Pneumatic dilation, 5% risk of perforation Injection of botulinum toxin into LES (temporary) Surgical myotomy POEM (peroral endoscopic myotomy)	Medical: aggressive GERD therapy (PPIs BID)	Reassurance that symptoms are not due to cardiac pain Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful), balloon dilatation

Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia
NEJM 2019;381:2219-2229
Purpose: To compare peroral endoscopic myotomy (POEM) to laparoscopic Heller's myotomy (LMH) in the treatment of achalasia.
Methods: Patients with symptomatic achalasia (n=221) were randomly assigned to either POEM or LMH. The primary endpoint was clinical success, while secondary endpoints included adverse events, esophageal function, Gastrointestinal Quality of Life (GQoL) score, and gastroesophageal reflux (GER).
Results: 83.0% of patients in the POEM group and 81.7% of patients in the LHM group achieved clinical success at 2 yr (P=0.007 for noninferiority). There was no difference in improvement of esophageal function or GQoL score between groups. Serious adverse events were observed in 2.7% and 7.3% of patients in the POEM and LHM groups, respectively. At 12 mo, 44% of patients in the POEM group and 29% of patients in the LHM group had reflux esophagitis.
Conclusions: POEM was noninferior to LHM in the treatment of symptomatic achalasia. GER was more common among patients who were treated with POEM than those treated with LHM.

Esophageal Diverticula

Definition
- outpouchings of one or more layers of the esophageal tract

Clinical Features
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

Classification
- pharyngoesophageal (Zenker's) diverticulum
  - most common form of esophageal diverticulum
  - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
  - symptoms: dysphagia, regurgitation of undigested food, halitosis (bad breath)
  - treatment: small and asymptomatic: no treatment required, large and symptomatic: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac

Peptic Stricture (from Esophagitis)

Definition
- a smooth, concentric narrowing most commonly seen in the lower esophagus

Clinical Features
- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops

Diagnosis
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

Treatment
- endoscopic dilatation and indefinite PPI

Esophageal Carcinoma

- see General Surgery and Thoracic Surgery, GS21

Webs and Rings

Definition
- web = partial occlusion by an eccentric, smooth extension of normal esophageal tissue, mucosa and submucosa (upper esophagus)
- ring = circumferential narrowing caused by an abnormal ring of tissue, congenital or acid-reflux induced (lower esophagus)

Clinical Features
- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Schatzki ring
  - mucosal ring at squamo-columnar junction
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic dilation

Infectious Esophagitis

Definition
- severe mucosal inflammation and ulceration as a result of a viral or fungal infection

Risk Factors
- DM
- chemotherapeutic agents
- immunocompromised states

Clinical Features
- characteristically odynophagia, less often dysphagia

Appearance
- *Candida* (most common): whitish-yellow plaques without visible ulceration or inflammation
- HSV (second most common), CMV: focal ulcers

Investigations
- diagnosis via endoscopic visualization and biopsy

Plummer-Vinson Syndrome Triad

Iron deficiency anemia

Dysphagia

Esophageal webs

Rare (prevalence <1 in 1000000) but good prognosis when treated with iron and esophageal dilatation

Eosinophilic Esophagitis

Eosinophils infiltrate the epithelium of the esophagus

Causes dysphagia, common cause of bolus food impaction

Usually primary, but can be part of the spectrum of eosinophilic gastroenteritis, secondary to drugs, parasites etc.

Often associated with allergies

Most characteristically occurs in young men

Diagnosis established by endoscopic biopsy, suggested by mucosal rings seen in the esophageal mucosa at endoscopy

Treatment: (a) diet (milk, soy, eggs, wheat, peanuts/tree nuts, and seafood), (b) PPI (c) swallowed topical corticosteroid (fluticasone or budesonide), (d) rarely prednisone

Treatment
- *Candida*: nystatin swish and swallow (for simple *Candida* infection), ketoconazole, fluconazole
- HSV: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV ganciclovir, famciclovir, or oral valganciclovir

Stomach and Duodenum

Dyspepsia

Definition
- predominant epigastric pain/burning lasting at least 1 mo
- other symptoms under umbrella of dyspepsia: post-prandial fullness, early satiety
- although the most common cause is functional (investigations show no organic disease but pain persists), sinister disease can present similarly (e.g. pancreatic cancer)

History and Physical Exam
- history: most important risk factors are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical exam: adenopathy, abdominal mass/organomegaly, Carnett's sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

Investigations
- consider blood tests including CBC, liver enzymes, calcium, *H. pylori* serology (Rome IV), and U/S
- gastroscopy to investigate dyspepsia: most causes of dyspepsia are either functional or diagnosable by either blood tests or PPI trial (for peptic disease); however, gastric cancer should not be missed. Gastroscopy recommended if ages ≥60 (and if ages <60 and under special circumstances such as risk factors for gastric cancer)

The most common cause of dyspepsia is functional (idiopathic) dyspepsia

Red Flags of Dyspepsia
(raise suspicion of gastric malignancy):
- Unintended weight loss
- Persistent vomiting
- Progressive dysphagia
- Odynophagia
- Unexplained anemia or iron deficiency
- Hematemesis
- Jaundice
- Palpable abdominal mass or lymphadenopathy
- Family history of upper GI cancer
- Previous gastric surgery

Stomach

Table 4. Cells of the Gastric Mucosa

Cell Type	Secretory Product	Important Notes
Parietal Cells	Gastric acid (HCl) and IF	Stimulated by histamine, acetylcholine (ACh), gastrin
Chief Cells	Pepsinogen	Stimulated by vagal input and local acid
D-Cells	Somatostatin	Inhibits release of hormones including gastrin
G-Cells	Gastrin	Stimulates H+ production from parietal cells
Superficial Epithelial Cells	Mucus, HCO_3^-	Protect gastric mucosa

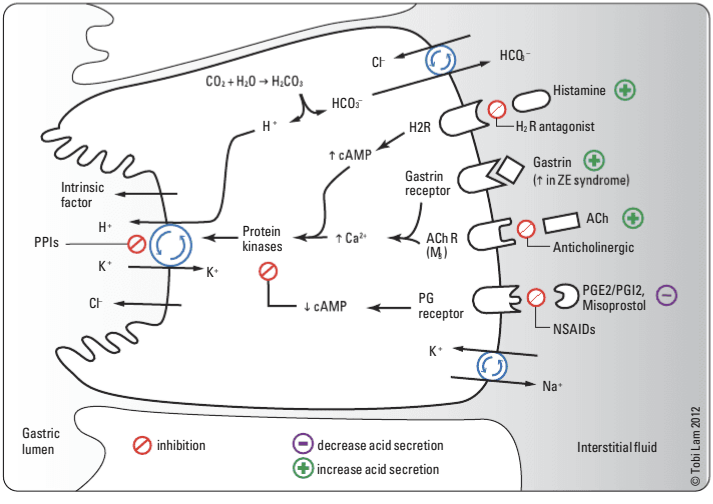


Figure 5. Stimulation of H+ secretion from the parietal cell

Gastritis

Definition

- defined histologically: inflammation of the stomach mucosa

Etiology

- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

Table 5. Updated Sydney Classification of Gastritis

Type	Common Etiology
Acute Gastritis	
Hemorrhagic/erosive gastritis	EtOH, Aspirin®/NSAID, shock/physiological stress (seen in ICU patients)
Helicobacter gastritis	*H. pylori*
Chronic Gastritis	
Non-atrophic	*H. pylori*
Atrophic	*H. pylori*, dietary, environmental factors (multi-focal), autoimmunity
Chemical	NSAID, bile
Radiation	Radiation injury
Lymphocytic	Celiac disease, drug
Eosinophilic	Food allergies
Non-infectious granulomatous	CD, sarcoidosis
Other infectious gastritides	Bacteria, viruses, fungi, parasite, TB, syphilis

Clinical Features

- non-erosive gastritis is asymptomatic (except with certain rare causes like CD), does not cause pain; difficult to diagnose clinically or endoscopically – requires biopsy for diagnosis
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

Treatment

- determined by etiology (see *H. pylori, G13, NSAID-Induced Ulceration, G13* and *Stress-Induced Ulceration, G14*)
- non-pharmacological: avoidance of mucosal irritants such as EtOH, NSAIDs, and foods that trigger symptoms

Peptic Ulcer Disease

Definition

- focal defects in the mucosa that penetrate the muscularis mucosa layer
- PUD includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

Etiology

Table 6. Etiology of PUD

	Duodenal	Gastric
***H. pylori* Infection**	90%	60%
NSAIDs	7%	35%
Physiologic Stress-Induced	<3%	<5%
Zollinger-Ellison Syndrome	<1%	<1%
Idiopathic	15%	10%

- NSAID negative, *H. pylori* negative ulcers becoming more commonly recognized as *H. pylori* prevalence decreases
- others: CMV (especially immunocompromised patients), ischemic, idiopathic
- EtOH: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with cigarette smoking, cirrhosis of liver, COPD, and chronic renal failure

Cigarette Smoking and PUD
Increased risk of ulcer
Increased risk of complications
Increased chance of death from ulcer
Impaired healing

Clinical Features

- dyspepsia: most common presenting symptom
  - only 5% of patients with dyspepsia have ulcers, while most have functional disease
  - however, 70% of peptic ulcers are asymptomatic
- may present with complications
  - bleeding 10% (severe if from gastroduodenal artery), perforation 2% (usually anterior ulcers), gastric outlet obstruction 2%
  - posterior inflammation (penetration) 2%; may also cause pancreatitis

- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters of weeks with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

Investigations

- endoscopy (most accurate)
- upper GI series
- *H. pylori* tests (see *Table 7, G13*)
- fasting serum gastrin measurement if Zollinger-Ellison syndrome suspected (but most common cause of elevated serum gastrin level is atrophic gastritis)

Gastric vs. Duodenal Ulcers
Most gastric ulcers require follow-up endoscopy with biopsy to rule out malignancies; duodenal ulcers are rarely malignant and therefore, do not usually warrant follow-up upper endoscopy to reassess ulcer status

Treatment

- specific management depends on etiology; (see *H. pylori, G13, NSAID-Induced Ulceration, G13* and *Stress-Induced Ulceration, G14*)
- treat *H. pylori* infection if present; eradication of infection prevents recurrence of PUD
- stop NSAIDs if possible
- start PPI: inhibits parietal cell H+/K+-ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other medications (e.g. histamine H2-antagonists) less effective
- smoking cessation
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, EtOH, and spices

Approach to PUD
Stop NSAIDs
Acid neutralization
H. pylori eradication
Quit smoking

Management of Bleeding Peptic Ulcers

- Gastroscopy (EGD) to explore upper GI tract
- IV pantoprazole
- establish risk of rebleeding/continuous bleed (since most ulcers stop bleeding spontaneously)
  - clinical risk factors: increased ages >60, bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
    - if ulcer possesses high-risk stigmata, then endoscopic therapy (e.g. clip) should be performed, consider ICU admission

Bleeding Peptic Ulcers
Risk Factors for Increased Mortality
Co-existent illness
Hemodynamic instability
Ages >60 yr
Transfusion required

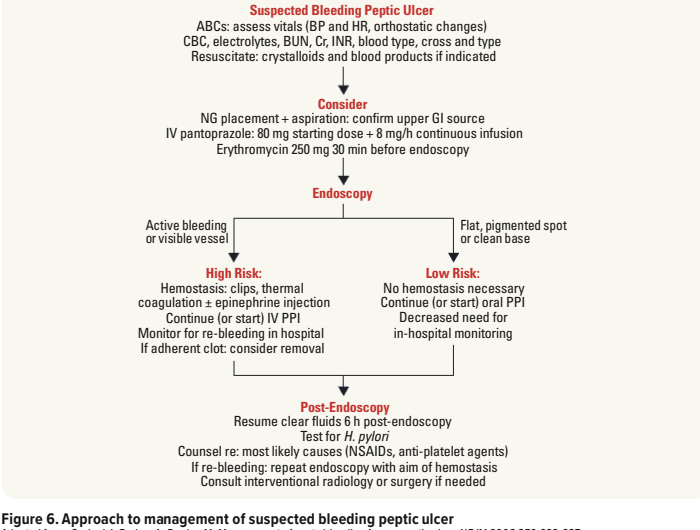

Suspected Bleeding Peptic Ulcer
ABCs: assess vitals (BP and HR, orthostatic changes)
CBC, electrolytes, BUN, Cr, INR, blood type, cross and type
Resuscitate: crystalloids and blood products if indicated
Consider
NG placement + aspiration: confirm upper GI source
IV pantoprazole: 80 mg starting dose + 8 mg/h continuous infusion
Erythromycin 250 mg 30 min before endoscopy
Endoscopy
Active bleeding or visible vessel
Flat, pigmented spot or clean base
High Risk:
Hemostasis: clips, thermal coagulation ± epinephrine injection
Continue (or start) IV PPI
Monitor for re-bleeding in hospital
If adherent clot: consider removal
Low Risk:
No hemostasis necessary
Continue (or start) oral PPI
Decreased need for in-hospital monitoring
Post-Endoscopy
Resume clear fluids 6 h post-endoscopy
Test for H. pylori
Counsel re: most likely causes (NSAIDs, anti-platelet agents)
If re-bleeding: repeat endoscopy with aim of hemostasis
Consult interventional radiology or surgery if needed

Figure 6. Approach to management of suspected bleeding peptic ulcer
Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937

H. pylori-Induced Peptic Ulceration

Pathophysiology

- *H. pylori*: Gram-negative flagellated rod that resides within the gastric mucosa, causing persistent infection and inflammation
- acid secreted by parietal cells (stimulated by vagal ACh, gastrin, histamine) necessary for most ulcers
- etiology of PUD secondary to *H. pylori* is not well understood; however, the pattern of colonization correlates with outcome
- gastritis only in antrum (15% of patients), high gastric acid, associated with duodenal ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
- gastritis throughout stomach ("pangastritis" – 85% of patients), low gastric acid, associated with stomach ulcer and cancer

Epidemiology

- *H. pylori* is found in about 20% of all Canadians, with increased prevalence in Indigenous populations and immigrants from high prevalence countries
- highest prevalence in those raised during 1930s
- infection most commonly acquired in childhood, presumably by fecal-oral route
- high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

Outcome

- gastritis (non-erosive) occurs in 100% of patients but is asymptomatic
- peptic ulcer in 15% of patients
- gastric carcinoma and mucosal associated lymphomatous tissue (MALT) lymphoma in 0.5% of patients
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children ages <5)

Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer
NEJM 2018;378:1085-1095
Purpose: To evaluate the role of H. pylori eradication in the prevention of metachronous gastric cancer.
Study: Double-blinded RCT.
Population: 470 patients with a subtotal gastrectomy for gastric cancer and H. pylori infection with or without ABx treatment.
Outcome: Incidence of metachronous gastric cancer.
Results: After almost 6 yr, 7.2% of the ABx-treated group developed another cancer in the gastric remnant vs. 13.4% in the placebo control group.
Conclusions: This provides definitive evidence that H. pylori is worthwhile treating no matter how advanced the gastric carcinogenic process.

Serology for *H. pylori* should not be used to check for eradication

Diagnosis

Table 7. Diagnosis of H. pylori Infection

Test	Sensitivity	Specificity	Comments
Non-invasive Tests			
Urea breath test	90-100%	89-100%	Affected by PPI therapy (false negatives)
Serology	88-99%	89-95%	Does not distinguish active vs. past infection; therefore, should not be used to assess post eradication status
Can remain positive after treatment			
Fecal antigen			Only rarely used in clinical practice
Invasive Tests (require endoscopy)			
Histology	93-99%	95-99%	Gold standard; affected by PPI therapy (false negatives)
Rapid urease test (on biopsy)	89-98%	93-100%	Rapid
Microbiology culture	98%	95-100%	Not widely available but can be used to determine ABx susceptibility. Research only

Treatment: *H. pylori* Eradication

- bismuth quadruple therapy recommended for 14 d: PPI (e.g. lansoprazole 30 mg BID) + bismuth 525 mg QID + metronidazole 500 mg QID + tetracycline 500 mg QID
- alternatively, concomitant non-bismuth quadruple therapy for 14 d: PPI + amoxicillin + metronidazole + clarithromycin

NSAID-Induced Ulceration

Pathophysiology

- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (IV NSAID causes ulcers, but not erosions)
  - NSAIDs also inhibit mucosal cyclooxygenase, leading to decreased prostaglandin synthesis
  - this results in ulcers from reduced secretion of protective bicarbonate and mucous, and decreased mucosal blood flow

Risk Factors for NSAID-induced Peptic Ulcer

- previous peptic ulcers/UGIB
- age (≥65 yr)
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

Clinical Features
- erosions may bleed, but usually only ulcers (which represent mucosal/submucosal injury) cause significant clinical problems
- most NSAID-induced ulcers are clinically asymptomatic: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulce
- may exacerbate underlying duodenal ulcer disease

Treatment
- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol (less effective) in one tablet
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration

If at high-risk for development of ulcers, prophylaxis with PPI indicated

Stress-Induced Ulceration

Definition
- ulceration or erosion in the upper GI tract of ill patients, usually in ICU (stress is physiological, not psychiatric)
- lesions most commonly in fundus of stomach

Pathophysiology
- injury to the mucosal barrier secondary to systemic stress resulting in multiple superficial erosions of the stomach
- commonly seen in patients with acute CNS injury (referred to as Cushing's ulcers) than other stress-related diseases (i.e. severe burns) (Curling's ulcers)
- etiology unclear - may involve ischemia / acid hypersecretion
- mechanical ventilation is the most important risk factor

Curling's and Cushing's Ulcers
Curling's Ulcer: acute peptic ulcer of the duodenum resulting as a complication from severe burns when reduced plasma volume leads to ischemia and cell necrosis (sloughing) of the gastric mucosa (think BURN from a CURLING iron)
Cushing's Ulcer: peptic ulcer produced by elevated ICP (may be due to stimulation of vagal nuclei secondary to elevated ICP which leads to increased secretion of gastric acid)

Risk Factors
- mechanical ventilation
- anti-coagulation
- multi-organ failure
- septicemia
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface

Clinical Features
- UGIB (see *Upper Gastrointestinal Bleeding, G28*)
- painless

Treatment
- prophylaxis with gastric acid suppressants decreases risk of UGIB; PPI most potent but may increase risk of pneumonia; H2 blockers less potent but less likely to cause pneumonia
- treat underlying cause, aggressive fluid resuscitation
- ulcer treatment same as for bleeding peptic ulcer, but often less successful

Gastric Carcinoma

- see General Surgery and Thoracic Surgery, GS26

Small and Large Bowel

Classification of Diarrhea

Definition
- clinically: diarrhea defined as stools that are looser and/or more frequent than normal (i.e. ≥3x/d); physiologically: 24 h stool weight >200 g (less useful clinically)

Classification
- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) vs. large volume (>1/2 cup stool; typical of small bowel diseases)
- watery: secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)
- steatorrhea
- inflammatory/transit or functional

Acute Diarrhea

• see Pediatrics, P43

Definition
• passage of ≥3 loose or liquid stools/d OR >200 g stool/d for >2 d but ≤14 d

Epidemiology
• one of the leading causes of death worldwide (about 88% of diarrhea associated deaths are caused by unsafe water, inadequate sanitation, and insufficient hygiene)
• significant morbidity in developed countries (over 900000 hospitalizations in the United States each year)

Etiology
• most commonly due to infections
• most infections are self-limiting and resolve within 7 d

Risk Factors
• food (raw or undercooked meat and seafood, unpasteurized dairy products)
• medications: ABx, laxatives
• others: high-risk sexual activity, infectious outbreaks, occupational exposures (daycare workers), family history (IBD)

Approach to Acute Diarrhea
• the most common cause of acute diarrhea is infectious
• in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
• investigations are costly and are necessary only in certain circumstances
  ▪ therefore, evaluation of acute diarrhea involves identifying characteristics of the patient or illness that warrant further investigation and assessing volume status to determine the most appropriate method of rehydration

Physical Exam
• volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
• abdominal exam: pain, guarding, peritoneal signs

Table 8. Classification of Acute Diarrhea

	Inflammatory	Non-Inflammatory
Definition	Disruption of intestinal mucosa	Intestinal mucosa intact
Site	Usually colon	Usually small intestine
Mechanism	Organisms and cytotoxins invade mucosa, resulting in the destruction of mucosal cells, and perpetuation of the diarrhea	Stimulation of intestinal water secretion and inhibition of water absorption (i.e. net secretion)
Sigmoidoscopy	Usually abnormal mucosa seen	Usually normal mucosa seen
Symptoms	Bloody (not always) Small volume, high frequency Often lower abdominal cramping with urgency ± tenesmus May have fever ± shock	Watery, little or no blood Large volume, low frequency Upper/periumbilical pain/cramping ± shock
Investigations	Fecal WBC and RBC positive	Fecal WBC negative
Etiology	See *Differential Diagnosis of Common Complaints, G4*	See *Differential Diagnosis of Common Complaints, G4*
Differential Diagnosis	Acute presentation of idiopathic IBD	Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease)
Significance	Higher yield with stool C&S Can progress to life-threatening megacolon, perforation, hemorrhage ABx may be helpful	Lower yield with stool C&S Chief life-threatening problem is electrolyte disturbances/ fluid depletion ABx unlikely to be helpful

Investigations
• stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (daycare worker, nursing home resident, community outbreaks, e.g. Walkerton, etc.)
  ▪ O&P takes up to three weeks to obtain the results
  ▪ C&S only tests *Campylobacter, Salmonella, Shigella, E. coli, Yersinia*
    ◆ other organisms must be ordered separately
• flexible sigmoidoscopy (without bowel preparation): useful if inflammatory diarrhea suspected
  ▪ histology (i.e. biopsies of mucosa) helps to distinguish idiopathic IBD (CD and UC) from infectious colitis or acute self-limited colitis
• *C. difficile* toxin: indicated in cases with recent/remote antibiotic use, hospitalization, nursing home living, or recent chemotherapy

Useful Questions in Acute Diarrhea

Those Fads Wilt
Travel
High-risk sexual activity (increased risk of fecal-oral exposure)
Outbreaks
Seafood
Extra intestinal signs of IBD
Family history
ABx
Diet
Steatorrhea
Weight loss
Immunosuppression
Laxatives
Tumour history

Infectious Causes of Inflammatory Diarrhea

Your **S**tool **S**mells **E**xtremely **C**rappy
***Y**ersinia*
***S**higella*
***S**almonella*
***E**. coli* (EHEC 0157:H7), ***E**. histolytica*
***C**ampylobacter*, ***C**. difficile*

An Update on the Role for Bacteriotherapy SER-109, an Oral Microbiome Therapy for Recurrent Clostridiodes difficile Infection
NEJM 2022;386:220-229
Building on the success of prior work demonstrating the efficacy of donor fecal transplant in patients with recurrent C. difficile infections, this randomized controlled trial shows that oral microbiome therapy (SER-109) effectively reduces the recurrence of C. difficile infection to 12% compared to 40% in cohorts receiving placebo. This trial along with similar prospective and retrospective work may standardize the use of medical probiotic therapy in patients with gastrointestinal disorders, including recurrent C. difficile infection.

Treatment

- fluid and electrolyte replacement orally in most cases, intravenously if severe extremes of age/coma
- antidiarrheals
  - antimotility agents: diphenoxylate, loperamide (Imodium®) should be used with caution; contraindicated in patients with mucosal inflammation, bloody diarrhea
  - side effects: abdominal cramps, toxic megacolon
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful (but should not be used in the presence of bloody diarrhea or fever)
- ABx: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially *Salmonella*)
    - drug side effects (including *C. difficile* infection)
    - development of resistant strains
    - renal failure/hemolysis (enterohemorrhagic *E. coli* O157:H7)
  - indications for antimicrobial agents in acute diarrhea
    - septicemia
    - prolonged fever with fecal blood (bloody diarrhea) or WBCs seen on O&P
    - clearly indicated: *Shigella, V. cholerae, C. difficile*, traveller's diarrhea (*E. coli* (ETEC)), *Giardia, Entamoeba histolytica, Cyclospora*
    - situational: *Salmonella, Campylobacter, Yersinia*, non-enterotoxigenic *E. coli*
    - *Salmonella*: always treat *Salmonella typhi* (typhoid or enteric fever); treat other *Salmonella* only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease
- report diarrheal illness to public health if appropriate

Causes of Acute Bloody Diarrhea

CHESS
C*ampylobacter*
H*emorrhagic E. coli (e.g. O157:H7)*
E*ntamoeba histolytica*
S*almonella*
S*higella*

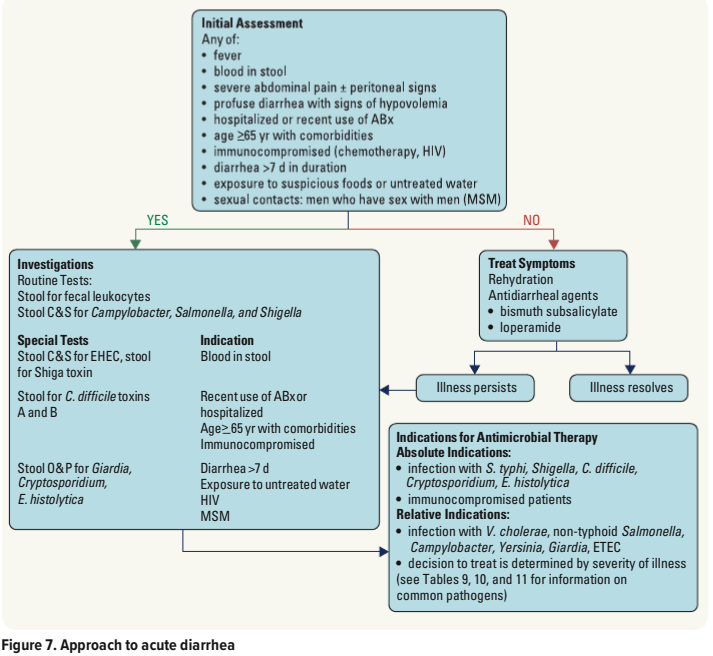

Initial Assessment
Any of:
• fever
• blood in stool
• severe abdominal pain ± peritoneal signs
• profuse diarrhea with signs of hypovolemia
• hospitalized or recent use of ABx
• age ≥65 yr with comorbidities
• immunocompromised (chemotherapy, HIV)
• diarrhea >7 d in duration
• exposure to suspicious foods or untreated water
• sexual contacts: men who have sex with men (MSM)
YES
NO
Investigations
Routine Tests:
Stool for fecal leukocytes
Stool C&S for Campylobacter, Salmonella, and Shigella
Special Tests
Indication
Stool C&S for EHEC, stool for Shiga toxin
Blood in stool
Stool for C. difficile toxins A and B
Recent use of ABx or hospitalized
Age≥65 yr with comorbidities
Immunocompromised
Stool O&P for Giardia, Cryptosporidium, E. histolytica
Diarrhea >7 d
Exposure to untreated water
HIV
MSM
Treat Symptoms
Rehydration
Antidiarrheal agents
• bismuth subsalicylate
• loperamide
Illness persists
Illness resolves
Indications for Antimicrobial Therapy
Absolute Indications:
• infection with S. typhi, Shigella, C. difficile, Cryptosporidium, E. histolytica
• immunocompromised patients
Relative Indications:
• infection with V. cholerae, non-typhoid Salmonella, Campylobacter, Yersinia, Giardia, ETEC
• decision to treat is determined by severity of illness (see Tables 9, 10, and 11 for information on common pathogens)

Figure 7. Approach to acute diarrhea

Note: S. typhi has a rose spot rash (transient maculopapular rash on anterior thorax, upper abdomen), and a prodrome of high fever, bradycardia, headache, and abdominal pain. Diarrhea is not the initial presentation

Table 9. Bacteria in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	Nausea/ Vomiting			
***B. cereus* – Type A (emetic)**	Rice dishes	1-6 h	–	–	–	+	<12 h	None	Preformed exotoxin
***B. cereus* – Type B (diarrheal)**	Meats, vegetables, dried beans, cereals	8-16 h	–	–	–	–	<24 h	None	Secondary endotoxin
Campylobacter jejuni	Uncooked meat, especially poultry	2-10 d	+	±	+	±	<1 wk	Macrolide or fluoroquinolone if diarrhea >1 wk, bloody diarrhea, or immunocompromised	Most common bacterial cause of diarrhea in Canada Associated with Guillain-Barré syndrome
Clostridium difficile	Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antimicrobials)	Unclear	±	±	±	–	Variable	Stop culprit antibiotic therapy if possible Supportive therapy (IV fluids) Empiric treatment with either vancomycin or fidaxomicin If access to empiric treatment is limited, then metronidazole may be used For fulminant *C. difficile* infection (previously called severe), oral vancomycin is used. IV metronidazole added to regimen if ileus present	Usually follows antibiotic treatment (especially clindamycin, fluoroquinolones, penicillins, cephalosporins) Can develop pseudomembranous colitis
Clostridium perfringens	Contaminated food, especially meat and poultry	8-12 h	±	–	+	–	<24 h	None	*Clostridium* spores are heat resistant Secondary enterotoxin Enteroinvasive
E. coli (EIEC)	Contaminated food/ water	1-3 d	+	±	+	–	7-10 d	None	Relatively uncommon Enterotoxigenic
E. coli (ETEC)	Contaminated food/ water	1-3 d	–	–	+	–	3 d	Fluoroquinolone or azithromycin for moderate to severe symptoms	Most common cause of traveller's diarrhea Heat-labile and heat-stable toxins
Enterohemorrhagic E. coli (EHEC/STEC) i.e. O157:H7	Contamination of hamburger, raw milk, drinking, and recreational water	3-8 d	–	+	+	±	5-10 d	None: ABx increase risk of HUS	Shiga toxin production Monitor renal function:10% develop HUS Antidiarrheals increase risk of HUS
***Salmonella Typhi S. Paratyphi* (i.e. Enteric Fever, Typhoid)**	Fecal-oral Contaminated food/ water Travel to endemic area	10-14 d	+	±	+	±	<5-7 d	Empiric treatment with ceftriaxone, ciprofloxacin, or azithromycin Fluoroquinolone resistance is increasing	*Salmonella typhi*: "Rose spot" rash (on anterior thorax, upper abdomen), fever, and abdominal pain precedes diarrhea
Non-typhoidal Salmonellosis *S. Typhimurium, S. Enteritidis*	Contaminated animal food products, especially eggs, poultry, meat, milk	12-72 h	+	±	+	+	3-7 d	Ciprofloxacin only in severe illness, extremes of age, joint prostheses, valvular heart disease, severe atherosclerosis, cancer, uremia	
Shigella dysenteriae	Fecal-oral Contaminated food/ water	1-4 d	+	±	+	+	<1 wk	Fluoroquinolone	Very small inoculum needed for infection Complications include toxic megacolon, HUS Antidiarrheals may increase risk of toxic megacolon
Staphylococcus aureus	Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)	2-4 h	–	–	+	+	1-2 d	None	Heat-stable preformed exotoxin
Vibrio cholerae	Contaminated food/ water, especially shellfish	1-3 d	–	–	–	+	3-7 d	Tetracycline or fluoroquinolones (ciprofloxacin)	Massive watery diarrhea (1-3 L/d) Mortality <1% with treatment
Yersinia	Contaminated food Unpasteurized milk	5 d	+	±	+	±	Up to 3 wk	Fluoroquinolone only for severe illness	Majority of cases in children 1-4 yr Mesenteric adenitis and terminal ileitis can occur without diarrhea, mimicking appendicitis Can also mimic CD of terminal ileum

Table 10. Parasites in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	Nausea/ Vomiting			
Cryptosporidium	Fecal-oral	7 d	±	–	–	+	1-20 d	Paromomycin + nitazoxanide	Immune reconstitution if immunosuppressed
Entamoeba histolytica	Worldwide endemic areas Fecal-oral	2-4 wk	±	+	–	+	Variable	Metronidazole + iodoquinol or paromomycin if symptomatic infection Only iodoquinol or paromomycin for asymptomatic cyst passage	If untreated, potential for liver abscess Sigmoidoscopy may show flat ulcers with yellow exudates
Giardia lamblia	Fecal-oral Contaminated food/ water	1-4 wk	–	–	+	+	Variable	Metronidazole or nitazoxanide Treatment of asymptomatic carriers NOT recommended	Higher risk in: daycare children, intake of untreated water ("beaver fever"), MSM, immunodeficiency (decreased IgA) May need duodenal biopsy

Table 11. Viruses in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	Nausea/ Vomiting			
Norovirus	Fecal-oral	24 h	–	–	+	+	24 h	None	Noroviruses include Norwalk virus
Rotavirus	Fecal-oral	2-4 d	±	–	–	±	3-8 d	None	Can cause severe dehydration Virtually all children are infected by 3 yr Oral vaccine given at 2 and 4 mo

Traveller's Diarrhea

Epidemiology

- most common illness to affect travellers
- up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

Etiology

- bacterial (80-90%): *E. coli* most common (ETEC), *Campylobacter, Shigella, Salmonella, Vibrio* (non-cholera); wide regional variation (e.g. *Campylobacter* more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): *Giardia, Entamoeba histolytica, Cryptosporidium*, and *Cyclospora* for ~10% in long-term travellers
- pathogen-negative traveller's diarrhea common despite exhaustive microbiological workup

Treatment

- rehydration is the mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss, use oral rehydration solutions (1 package in 1 L boiled or treated water)
- treat symptoms: antidiarrheal agents (e.g. rifamycin ABx, bismuth subsalicylate, loperamide)
- empiric ABx in moderate or severe illness: ciprofloxacin, azithromycin, or rifaximin

note: there is increasing fluoroquinolone resistance in causative agents, especially in South and Southeast Asia

Prevention

- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
- bismuth subsalicylate (Pepto-Bismol®): 60% effective (2 tablets QID)
- antibiotic prophylaxis not recommended
  - increased risk of infection with resistant organisms
  - high-risk groups (e.g. immunocompromised individuals) likely to be infected with pathogen not covered by standard antimicrobial agents

- Dukoral®: oral vaccine that offers protection against *V. cholerae* (efficacy ~80%) and ETEC (efficacy ~50-67%)
  - 2 doses should be taken 2 wk prior to traveling and the effect may last up to 3 mo
  - Public Health Agency of Canada recommends that it may be considered for the following situations (not recommended for routine use in travellers):
    - increased risk of acquiring traveller's diarrhea (gastric hypochlorhydria or young children >2 yr)
    - short-term travellers who are high-risk (e.g. chronic illness) and have an increased risk of serious consequences of traveller's diarrhea (e.g. chronic renal failure, CHF, T1DM, IBD)
    - immunosuppression
    - history of repeat traveller's diarrhea
    - travellers to cholera endemic countries at increased risk of exposure
- two vaccines against *Salmonella typhi* are available and their effectiveness is estimated to be 50-70%

Chronic Diarrhea

Definition
- passage of frequent unformed stool for >4 wk (compared to persistent diarrhea lasting 14-30 d)

Etiology/Classification
- majority of cases are non-infectious
- see *Differential Diagnosis of Common Complaints, G5*

Investigations
- guided by history
- stool analysis for: *C. difficile* toxin, C&S, O&P ± fecal fat, WBC, fecal calprotectin
- blood for: CBC, electrolytes, C-reactive protein (CRP) , TSH, celiac serology (IgA anti-tTG; ask for serum protein electrophoresis or immunoglobulin quantitation to rule out IgA deficiency, which has an increased frequency in celiac disease)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (low yield)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease

Treatment
- approach is similar to that of acute diarrhea
- dependent on underlying etiology

Maldigestion and Malabsorption

Definition
- maldigestion: inability to break down large molecules in the lumen of the intestine into their component small molecules
- malabsorption: inability to transport molecules across the intestinal mucosa into circulation

Etiology
- maldigestion
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis (CF) (remember CF can result in pancreatic exocrine insufficiency as well), pancreatitis, cancer)
  - bile salt deficiency
    - terminal ileal disease (impaired enterohepatic recycling in view of loss greater than synthesis), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic, e.g. PBC)
  - specific enzyme deficiencies (e.g. lactase)
- malabsorption
  - inadequate absorptive surface
    - infections/infestations (e.g. Whipple's disease, *Giardia*)
    - immunologic (e.g. celiac disease)
    - infiltration (e.g. lymphoma, amyloidosis)
    - fibrosis (e.g. systemic sclerosis, radiation enteritis): can lead to loss of surface area but also areas of stricture formation resulting in stasis with small bowel overgrowth
    - small bowel resection (length, site, location, presence/absence of ileocecal valve, and integrity of colon are important)
    - congenital (e.g. short bowel syndrome)
    - inflammatory: extensive ileal CD (pivotal number is 100 cm as <100 cm = bile salt or choleretic diarrhea, >100 cm = fatty diarrhea or steatorrhea)

- drug-induced
  - cholestyramine, ethanol, neomycin, tetracycline, and other ABx
- endocrine
  - DM (complex pathogenesis)

Fat Soluble Vitamins: ADEK
vitamin **A**, vitamin **D**, vitamin **E**, vitamin **K**

Clinical Features

- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency

Table 12. Absorption of Nutrients and Fat Soluble Vitamins

Deficiency	Absorption	Clinical Disease and/or Features	Investigations
Iron	Duodenum, upper jejunum	Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica	↓ Hb, ↓ serum Fe, ↓ serum ferritin
Calcium	Duodenum, upper jejunum (binds to Ca^{2+} binding-protein in cells; levels increased by vitamin D)	Metabolic bone disease, may get tetany and paresthesias if serum calcium falls* (see Endocrinology, E42)	↓ Serum Ca^{2+}, ↓ serum Mg^{2+}, and ↑ ALP Evaluate for ↓ bone mineralization radiographically (dual energy x-ray absorptiometry, DEXA)
Folic Acid	Jejunum	Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)	↓ Serum folic acid
Vitamin B_{12}	B_{12} ingested and bound to R proteins mainly from salivary glands; stomach secretes IF in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B_{12}-IF complex forms, protecting B_{12} from further protease attack; B12 absorbed in ileum and binds to transcobalamin (TC)	Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis	Differentiate causes by nuclear Schilling test (when available) Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H25)
Carbohydrate	Complex polysaccharides hydrolyzed to oligosaccharides and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum	Generalized malnutrition, weight loss, flatus, and diarrhea	Hydrogen breath test Trial of carbohydrate-restricted diet D-xylose test
Protein	Digestion begins in stomach, then brush border, and inside cell Absorption occurs primarily in the jejunum	General malnutrition and weight loss, amenorrhea, and ↓ libido if severe	↓ Serum albumin (low sensitivity)
Fat	Lipase, colipase, phospholipase A (pancreatic enzymes), and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Absorption occurs primarily in the jejunum Fatty acids diffuse into cell cytoplasm	Generalized malnutrition, weight loss, and diarrhea Foul-smelling feces + gas Steatorrhea	Small bowel biopsy MRCP, ERCP, pancreatic function tests (not routinely available) Quantitative stool fat test (72 h) May start with qualitative stool fat test (Sudan stain of stool) C-triolein breath test (not routinely available)
Vitamin A	Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)	Night blindness Dry skin Keratomalacia	
Vitamin D	Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)	Osteomalacia in adults Rickets in children	
Vitamin E	Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)	Retinopathy, neurological problems	
Vitamin K	Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum ABx and/or starvation	Prolonged INR may cause bleeding	

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone

Investigations

- tTG-IgA antibody serology/immunoglobulin A quantitation and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea (gold standard)
- fecal elastase to screen for pancreatic insufficiency and/or consider empiric trial of pancreatic enzymes based on clinical context
- serum carotene (precursor to vitamin A), folate, Ca^{2+}, Mg^{2+}, vitamin B_{12}, albumin, ferritin, serum iron solution, international normalized ratio/partial thromboplastin time (INR/PTT)
- stool fat globules on fecal smear stained with Sudan (used as an initial qualitative screening tool)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)

Treatment

- dependent on underlying etiology

Celiac Disease (Gluten Enteropathy/Sprue)

Definition
- abnormal small intestine mucosa due to intestinal reaction to gluten, a protein found in wheat, barley, rye, and possibly oats (certified gluten-free oats may be acceptable in a subgroup of patients)

Etiology
- unique autoimmune disease because the genetics (HLA-DQ2/8), the auto-antigen (tTG), and the environmental trigger (gluten) are all known
- associated with other autoimmune diseases, especially Sjögren's, T1DM, thyroid disease
- gluten is broken down to gliadin, which is the toxic protein
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared to 20% of the general population; celiac also associated with HLA-DQ8
- HLA-DQ2/Q8 are necessary permissive genes, but their presence does not confer a diagnosis of celiac disease (note: up to 40% of White individuals carry the HLA alleles, but will never develop celiac disease)

Epidemiology
- more common in women
- prevalence: 1 first degree relative: 10%; 2 first degree relatives: 20%
- may present any time in life, with peak presentation in infancy (when cereals introduced)

Clinical Features
- classic presentation: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; more common current presentation: bloating, gas, iron deficiency, or asymptomatic (patient at risk)
- improves with gluten-free diet, disease exacerbation when gluten reintroduced
- disease is usually most severe in proximal bowel
  - iron, calcium, and folic acid deficiency (absorbed in proximal small bowel) more common than vitamin B_{12} deficiency (absorbed in distal small bowel or ileum)
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

Investigations
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - patients with selective IgA deficiency have false-negative anti-tTG
    - therefore, measure serum IgA concomitantly (via serum immunoglobulin quantitation)
- incorporate serum testing tTG and/or DGP IgG in IgA deficiencies
- small bowel mucosal biopsy (usually duodenum) is diagnostic:
  - increased intraepithelial lymphocytes (earliest pathologic finding)
  - crypt hyperplasia (next stage of pathophysiology)
  - villous atrophy (last stage of pathophysiology)
  - note: there is a wide differential diagnosis for villous atrophy, including, but not limited to, small bowel overgrowth, CD, lymphoma, Giardia, HIV
- improvement with a gluten-free diet, but should not be started before serological tests and biopsy
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, Ca^{2+}, Fe, albumin, cholesterol, carotene, B_{12} absorption
- quantitative fecal fat >7%

Treatment
- dietary counselling
  - gluten free diet; avoid barley, rye, wheat (as these grains are related and have toxic proteins, similar to gliadin)
  - oats allowed if not contaminated by other grains (grown in soil without cross-contamination)
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
- if poor response to diet change, consider
  - alternate diagnosis
  - non-adherence to gluten-free diet (advertent or inadvertent)
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
  - development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
  - development of diffuse jejunal ileal intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)

Early Gluten Introduction and Celiac Disease in the EAT Study: A Prespecified Analysis of the EAT Randomized Clinical Trial
JAMA Pediatr 2020;174:1-7
Purpose: Determine whether introduction of high-dose gluten lowers celiac disease prevalence at 3 yr of age
Methods: Infants were randomized to consume 6 allergenic foods in addition to breast milk from age 4 mo (early introduction), or to avoid allergenic foods and follow exclusive breastfeeding guidelines (standard introduction). Evaluation of celiac disease was an a priori secondary outcome of the EAT trial, tested at age 3 with anti transglutaminase 2 antibodies.
Results: 1.4% of infants in the standard introduction group had a celiac disease diagnosis confirmed, versus 0% of infants in the early introduction group.
Conclusion: Introduction of gluten from age 4 mo was associated with a reduction in the prevalence of celiac disease.

Gluten Found in BROW

Barley
Rye
Oats (controversial)
Wheat

Prognosis
- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon; slight increase compared with general population), autoimmune diseases
- risk of lymphoma may be lowered by dietary gluten restriction

Inflammatory Bowel Disease

Definition
- group of disorders characterized by inflammation, and potentially ulceration, of the gastrointestinal tract; two main forms include CD and UC

Etiology
- complex, multifactorial etiology
- most likely a sustained response of the immune system, perhaps to enteric flora
- lack of appropriate down-regulation of immune responsiveness after an infection in a genetically predisposed individual

Genetics
- increased risk of both UC and CD in relatives of patients with either disease, especially siblings; early onset disease
  - familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 200+ associated gene loci
- CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially in Ashkenazi Jews, early onset disease, ileal involvement, and fistulizing, fibrostenotic, or stricturing disease
  - *CARD15* gene product modulates NFκβ, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

Clinical Features

Table 13. Clinical Differentiation of Ulcerative Colitis from Crohn's Disease

	Crohn's Disease	Ulcerative Colitis
Location	Any part of GI tract ("gum to bum") Small bowel + colon: 50% Small bowel only: 30% Colon only: 20%	Isolated to large bowel Always involves rectum, may progress proximally
Rectal Bleeding	Uncommon; possible if colonic disease	Very common (90%)
Diarrhea	Usually non-bloody (may be bloody, particularly if distal colon is involved)	Frequent, mucous, bloody, small volume stools
Abdominal Pain	Post-prandial/colicky	Predefecation/colicky
Fever	Common	Uncommon
Urgency/Tenesmus	Uncommon (unless rectum involved)	Common
Palpable Mass	Frequent (25%), RLQ	Rare (if present, often related to cecum full of stool)
Recurrence After Surgery	Common	None post-colectomy (with permanent ileostomy)
Endoscopic Features	Segmental inflammation, ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning	Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps
Histologic Features	Transmural distribution with skip lesions Focal inflammation ± Noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures Glands intact	Mucosal distribution, continuous disease (no skip lesions) Architectural distortion, gland disruption, crypt abscess Granulomas absent
Radiologic Features	Cobblestone mucosa Frequent strictures and fistulae Abdominal x-ray: bowel wall thickening, "string sign"	Lack of haustra Strictures rare; if present, need to rule out complicating cancer
Complications	Strictures, fistulae, perianal disease	Toxic megacolon
Colon Cancer Risk	Increased if >30% of colon involved	Increased except in proctitis

Table 14. Extraintestinal Manifestations of IBD

System	Crohn's Disease	Ulcerative Colitis
Dermatologic		
Erythema nodosum	15%	10%
Pyoderma gangrenosum	10%	Less common
Perianal skin tags	75-80%	Rare
Oral mucosal lesions, stomatitis	Common	Rare
Psoriasis	Present in 5-10% of those with IBD but not an EIM	
Rheumatologic		
Peripheral arthritis	15-20% of those with IBD (CD>UC)	
Ankylosing spondylitis	10% of those with IBD (CD>UC)	
Sacroiliitis	Occurs equally in CD and UC	
Ocular (~10% of IBD)		
Uveitis (vision threatening)		
Episcleritis (benign)	3-4% of IBD patients (CD>UC)	
Hepatobiliary		
Cholelithiasis	15-35% of patients with ileal CD	
PSC	1-5% of IBD cases with colonic involvement	
Fatty liver		
Gallstones	Pigment stones in CD	
Urologic		
Calculi	Most common in CD, especially following ileal resection or extensive terminal ileal disease (oxalate stones), in context of an intact colon	
Ureteric obstruction		
Fistulae	Characteristic of CD	
Others		
Thromboembolism		
Vasculitis		
Osteoporosis	Increased in CD with/without prior steroids, in UC only after steroids usage	
Vitamin deficiencies (B_{12}, ADEK)		
Cardiopulmonary disorders		
Pancreatitis (rare)		
Phlebitis		

Crohn's Disease

Definition

- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region ("gum to bum")

Epidemiology

- worldwide incidence 3-15 to 10-20/100000; 135000 Canadians living with CD
- bimodal: onset before age 30, second smaller peak at age 60; M=F
- incidence of CD increasing (relative to UC) especially in young females
- more common in White people, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in CD patients is higher than general population

Pathology

- most common location: ileum + right colon
- linear ulcers leading, when in clusters, connect and form mucosal islands or a "cobblestone" appearance
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

Clinical Features

- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- commonly presents as recurrent episodes of abdominal cramps, diarrhea (with or without bleeding), fatigue, and weight loss
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- EIMs are more common with colonic involvement
- fistulae, fissures, abscesses are common
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina, and other parts of bowel

Effect of Tight Control Management on Crohn's Disease (CALM): A Multi-Centre, Randomized Controlled Phase 3 Trial
Lancet 2017; 390:2779-2789
Purpose: To define the role of incorporating laboratory biomarkers in the management algorithm of active CD.
Study: RCT
Population: 224 adult patients (22 countries at 74 hospitals) with active CD were randomized to intensify treatment based on either laboratory biomarkers (serum CRP, fecal calprotectin) plus clinical evaluation (CD activity index and prednisone use) or treatment based on clinical evaluation alone.
Outcomes: Mucosal healing via the absence of deep ulcers.
Results: At 2 yr, more patients receiving treatment criteria that included laboratory tests had complete mucosal healing (i.e. no ulcers) than the group treated on the basis of symptoms alone (46% vs. 30%). Admittedly, the endpoint of mucosal healing is not a strong clinically relevant result, but other studies have shown that the greater the mucosal ulceration, the higher the rate of complications (i.e. strictures, fistulae, abscesses, hospitalizations, and surgery).
Conclusions: This is not definitive data but adds to other evidence showing that the traditional management paradigm needs revising, so in most patients it is worthwhile aiming for endoscopic healing of CD irrespective of symptoms.

Investigations
- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response (especially acutely in UC)
- bacterial cultures, O&P, *C. difficile* toxin to exclude other causes of inflammatory diarrhea

Management (see Figure 8)

Table 15. Management of Crohn's Disease

Management	Notes
Lifestyle/Diet	Smoking cessation Fluids only during acute exacerbation Enteral diets may aid in remission only for Crohn's ileitis, not colitis No evidence for any non-enteral diet changing the natural history of CD, but may affect symptoms Those with extensive small bowel involvement or extensive resection require electrolyte, mineral, and vitamin supplements (vitamin D, Ca^{2+}, Mg^{2+}, Zn, Fe, B_{12})
Antidiarrheal Agents*	Loperamide (Imodium®) > diphenoxylate (Lomotil®) > codeine (cheap but addictive) All work by decreasing small bowel motility, used only for symptom relief CAUTION: if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups
5-ASA**	Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine Hydrolysis by intestinal bacteria releases 5-ASA (active component) Dose-dependent efficacy Mesalamine (Pentasa®, Salofalk®, Mezavant®, Olsalazine®): used for the treatment of mild ileitis (CD) and mild UC, when inflammation is mild
Antibiotics	E.g. metronidazole (20 mg/kg/d, BID or TID dosing) or ciprofloxacin Best described for perianal CD, although characteristically relapse when discontinued
Corticosteroids	Prednisone: starting dose 40 mg once daily for acute exacerbations of colon-only CD; Budesonide: (first pass metabolism corticosteroid) 9 mg once daily for acute exacerbations of terminal ileum ± right colon CD; IV methylprednisolone if severe No proven role for steroids in maintaining remission; masks intra-abdominal sepsis
Immunosuppressives	6-mercaptopurine (6-MP), azathioprine (Imuran®); MTX (used less often) More often used to maintain remission than to treat active inflammation Most commonly used as steroid-sparing agents i.e. to lower risk of relapse as corticosteroids are withdrawn Usually requires >3 mo to have beneficial effect; usually continued for several years May help to heal fistulae, decrease disease activity Increases efficacy of biologics, plus lowers chances of biologic dosing efficacy (tolerance) - may be used in combination (dual therapy) with biologics Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy (i.e. lymphoma)
Biologics	Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α Proven effective for treatment of fistulae and medically refractory CD First-line immunosuppressive therapy with infliximab + azathioprine (dual therapy) more effective than using either alone (monotherapy) Ustekinumab, monoclonal antibody against P40 subunit of interleukin 12 and 23 Vedolizumab, monoclonal antibody directed against integrin α4β7 thereby reducing lymphocyte traffic to gut – now indicated for UC and CD
Immunotherapy (Small molecules)	JAK (Janus Kinase) inhibitors (e.g. tofacitinib). Efficacy demonstrated in UC
Surgical/ Experimental	Surgical treatment (see General and Thoracic Surgery, GS36) Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding, and for medically refractory disease If <50% or <200 cm of functional small intestine, risk of short bowel syndrome At least 50% clinical recurrence within 5 yr; 85% within 15 yr; endoscopic recurrence rate even higher 40% likelihood of second bowel resection, 30% likelihood of third bowel resection Complications of ileal resection <100 cm resected → watery diarrhea or cholorrhea (impaired bile salt absorption) Treatment: cholestyramine or antidiarrheals, e.g. loperamide >100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency) Treatment: fat restriction, medium chain triglycerides

*Cholestyramine: a bile-salt binding resin; for watery diarrhea with <100 cm of terminal ileum diseased or resected; however, non-specific antidiarrheals are more convenient and often more potent
**5-ASA use in CD is controversial; however, initial trial for mild ileitis only is warranted (induction and maintenance if clinical response)

Traditional Medical Management of Crohn's Disease

	Induction of Remission	Maintenance
5-ASA*	?	?
Steroids	+	
Immuno-modulators (e.g. azathioprine, methotrexate (MTX))	-	+
Antibiotics	+	
Biologics	+	+

*5-aminosalicylic acid (5-ASA) use in CD is controversial. However, initial trial for mild ileitis only is warranted (induction and maintenance if clinical response)

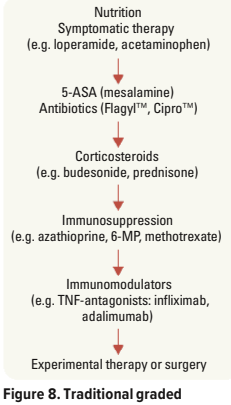


Figure 8. Traditional graded approach to induction therapy in Crohn's disease
Note: immunosuppressants and immunomodulators are increasingly used initially ("top-down management strategy"), 5-ASA drugs have limited role in Crohn's disease

Prognosis
- highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- complications include
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as UC (see *Ulcerative Colitis, G25*) if more than 1/3 of colon involved

Ulcerative Colitis

Definition
- inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

Epidemiology
- worldwide incidence 3-15 to 10-20/100000; 120000 Canadians living with UC (less common than CD)
- 2/3 onset by age 30 (with second peak after 50 yr); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- reduced risk in smokers
- inflammation limited to rectum or left colon is more common than pancolitis

Pathology
- disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
- inflammation is diffuse, continuous, and confined to mucosa

Clinical Features
- rectal bleeding is the hallmark feature; diarrhea present if more than the rectum is involved
  - can also have abdominal cramps/pain, especially with defecation
- severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
- tenesmus, urgency, incontinence
- systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
- EIMs (see *Table 14, G23*)
- characteristic exacerbations and remissions; 5% of cases are fulminant

Investigations
- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel preparation often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- occasionally CT colonography (formerly barium enema) to complete evaluation of colon if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, *C. difficile* toxin assay necessary to exclude infection
- no single confirmatory test

Treatment
- mainstays of treatment: 5-ASA derivatives (only in mild to moderate disease) and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- there is no specific diet to decrease inflammation; however, during a flare-up, elimination of dairy products may alleviate symptoms
- antidiarrheal medications generally not indicated in UC
- 5-ASA
  - topical (suppository or enema): effective for distal disease (rectum to splenic flexure) if inflammation is mild, preferable to corticosteroids
  - oral: effective for mild to moderate, but not severe colitis (e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d)
  - commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
  - may decrease rate of colorectal cancer
- corticosteroids
  - to remit acute disease, especially if severe or first attack; may need IV steroids initially (e.g. methylprednisolone 20 to 30 mg IV q12 h)
  - limited role as maintenance therapy for mild to moderate disease
  - for mild to moderate disease, may use oral Budesonide -CR (colonic extended release formulation)
  - use suppositories (predominantly available in compound pharmacies) for proctitis
  - use enemas and topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants / immunobiologics / immunotherapy(steroid-sparing)
  - in hospitalized patients with severe UC – add IV infliximab if no response to IV methylprednisolone within 3 d; then consider colectomy if inadequate response
  - immunosuppressant: azathioprine and 6-MP: too slow to rapidly resolve acute relapse
    - most commonly used to maintain remission as corticosteroids withdrawn
    - given with biologics: increase efficacy of infliximab and decrease likelihood of developing tolerance to infliximab (~10% chance/yr)
  - biologics (infliximab, adalimumab, golimumab, vedolizumab) can be used for outpatients with moderate-severe disease, particularly those that are steroid-unresponsive or steroid-dependent, some evidence that they are best used early in course of disease
- immunotherapy:
  - tofacitinib, upadacitinib: JAK-inhibitors, non-selective and gut selective respectively, can also be used for outpatients with moderate-severe disease, with failure to other biologic agents, steroid-unresponsive or steroid-dependent
  - ozanimod: an oral sphingosine-1-phosphate receptor modulator used for treating moderate-to severe UC
    - does not require previous failure of immunosuppressants, glucocorticoids, biologics, or other small molecules
    - increases clinical remission rates compared to placebo

In UC, non-bloody diarrhea is frequently the initial presentation; eventually progressing to bloody diarrhea

Medical Management of Ulcerative Colitis

	Induction of Remission	Maintenance
5-ASA	+	+
Steroids	+	
Immuno-suppressive	±	+

- surgical treatment (restorative)
  - aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastomosis (IPAA)
  - indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids, overt malignancy

Complications
- similar to CD, except:
  - more liver problems (especially PSC in men)
  - greater risk of colorectal cancer
    - risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%)
    - risk is increased in patients with chronic, active mucosal inflammation
    - thus, regular colonoscopy with surveillance biopsies and or chromoendoscopy is indicated in pancolitis of ≥8 yr is indicated
    - patients with coincident liver disease, PSC have a 5-fold risk of colon cancer versus those with UC alone. Patients with UC and PSC require annual surveillance colonoscopy with biopsy and or chromoendoscopy annually
    - patients with proctitis alone have the same risk for colon cancer as the general population
  - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery and Thoracic Surgery, GS45)

When Considering Complications of IBD, Think:

ULCERATIVE COLITIS
Urinary calculi
Liver problems
Cholelithiasis
Epithelial problems
Retardation of growth/sexual maturation
Arthralgias
Thrombophlebitis
Iatrogenic complications
Vitamin deficiencies
Eyes
Colorectal cancer
Obstruction
Leakage (perforation)
Iron deficiency
Toxic megacolon
Inanition (wasting)
Strictures

Prognosis
- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st yr correlates with increased severity of attacks and increased colectomy rate
  - colectomy rate = 1% for all patients after the 1st yr; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course, lifetime risk of extension is 15%
- fecal calprotein is a useful stool surrogate marker of bowel mucosal inflammation, that can be utilized as a follow-up marker for disease activity

Irritable Bowel Syndrome

Definition
- a form of functional bowel disease, now also known as disorder of gut-brain interaction; more than just a label for GI symptoms unexplained after normal investigations

Epidemiology
- 11% worldwide prevalence
- onset of symptoms usually in young adulthood
- F>M

Clinical Features
- Rome IV Criteria are used for diagnosis
- diagnosis is based chiefly on history; no specific diagnostic test available

Pathophysiology
- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associated or causative
- psychological: stress may increase IBS symptoms but probably does not cause IBS
- 4 main types of IBS
  - IBS-D: IBS with predominant diarrhea
  - IBS-C: IBS with predominant constipation
  - IBS-M: IBS-mixed with both diarrhea and constipation (each >25% of all abnormal bowel movements)
  - IBS untyped: insufficient abnormalities to be IBS-C, D, or M

Emerging Biologic Treatments for Ulcerative Colitis

Generic Name	Brand Name	Major Study
Ustekinumab	Stelara™	NEJM 2019; 381:1201-1214
Vedolizumab	Entyvio™	NEJM 2019; 381:1215-1226
Adalimumab	Humira™	NEJM 2019; 381:1215-1226

Diagnosis

Table 16. Rome IV Criteria for Diagnosing Irritable Bowel Syndrome

IBS Rome IV Criteria	
Recurrent abdominal pain for more than 6 mo, at least 1 d/wk in the last 3 mo, associated with 2 or more of the following: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool	
Symptom onset at least 6 mo before diagnosis and criteria present during the last 3 mo	
The following are supportive, but not essential to the diagnosis: Abnormal stool frequency (>3/d or <3/wk) Abnormal stool form (lumpy/hard/loose/watery) >1/4 of defecations Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) >1/4 of defecations Passage of mucus >1/4 of defecations Bloating	
Diagnosis of IBS Less Likely in Presence of "Red Flag" Features	
Weight loss Fever Nocturnal defecation	Anemia Blood or pus in stool Abnormal gross findings on flexible sigmoidoscopy
Normal Physical Exam	

Investigations
- if history consistent with Rome IV criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS, particularly celiac disease and IBD
- investigations can be limited to CBC and celiac serology
- if available, fecal calprotectin is likely more reliable test to rule out IBD
- consider TSH, stool cultures depending on clinical circumstances
- consider colonoscopy (e.g. if alarm features present, family history of IBD, or age >50)

IBS Mimickers
Enteric infections e.g. Giardia
Lactose intolerance/other disaccharidase deficiency
CD
Celiac sprue
Drug-induced diarrhea
Diet-induced (excess tea, coffee, colas)

Treatment
- education: reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction, cognitive behavioural therapy, probably exercise
- dietary: low FODMAP (Fermentable Oligo-, Di-, Monosaccharides And Polyols) diet for pain, bloating, gas, irregular bowel movements (BMs)
- no therapeutic agent consistently effective, pain most difficult to control, no drug changes natural history so the drug should be "wanted, since it is not needed"
- symptom-guided treatment
  - pain predominant
    - antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine - low level of evidence)
    - tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) - moderate level of evidence
  - IBS-D
    - increase fibre (bran or psyllium) to increase stool consistency but may worsen abdominal gas (controversial)
    - loperamide (Imodium®) (continuous use not recommended)
    - diphenoxylate (Lomotil®)
    - eluxadoline
    - rifaximin
  - IBS-C
    - increase fibre in diet
    - linaclotide, plecanatide, tenapanor
    - osmotic or other laxatives (help more with the constipation than the pain)

Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation
NEJM 2011;364:22-32
Purpose: Previous evidence suggests that gut flora may play an important role in the pathophysiology of IBS. This study evaluated rifaximin, a minimally absorbed antibiotic, in treating IBS without constipation.
Methods: Two phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2). 1260 patients who had IBS without constipation were randomly assigned to rifaximin (550 mg dose) or placebo, TID for 2 wk, with a follow-up of 10 wk. The primary endpoint was adequate self-reported relief of global IBS symptoms.
Results: Significantly more patients in the rifaximin group had adequate self-reported relief of global IBS symptoms compared to the placebo group during the first 4 wk after treatment (40.8% vs. 31.2%, respectively). Also, more patients in the rifaximin group had adequate relief of bloating compared to the placebo group (39.5% vs. 28.7%, respectively).
Conclusions: Rifaximin therapy for 2 wk provided significant relief of symptoms, bloating, abdominal pain, and stool consistency associated with IBS without constipation.

Prognosis
- 80% improve over time
- most have intermittent episodes
- normal life expectancy

Constipation

Definition
- passage of infrequent/hard stools and/or difficult stool evacuation (e.g. straining, sensation of anorectal blockage)

Epidemiology
- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries

Etiology
- most common: functional, idiopathic attributed to colon dysmotility but this is difficult to measure
- organic causes: likely only if there are symptoms other than constipation
  - medication side effects (e.g. narcotics, antidepressants) are the most common

Causes of Constipation

DOPED
Drugs
Obstruction
Pain
Endocrine dysfunction
Depression

- intestinal obstruction, left sided colon cancer (consider in older patients), and fecal impaction
- metabolic
  - DM
  - hypothyroidism
  - hypercalcemia, hypokalemia, uremia
- neurologic
  - intestinal pseudo-obstruction
  - Parkinson's disease
  - MS
- collagen vascular disease (e.g. scleroderma)
- painful anal conditions (e.g. fissures)

Clinical Features
- overlaps with IBS with constipation (IBS-C) but labeled as IBS-C when pain is a predominant feature
- stool firm, difficult to expel, passed with straining, abdominal pain relieved by defecation, flatulence, overflow diarrhea, tenesmus, abdominal distension, infrequent BMs (<3/wk)

Investigations
- underlying disease rarely found if constipation is the only presenting symptom
  - only test indicated in this situation is a CBC (2013 recommendation of American Gastroenterology Association), but also consider TSH, calcium, glucose, and abdominal x-ray
- colon visualization (colonoscopy, CT colonography) if concomitant symptoms such as rectal bleeding, weight loss, anemia or age >50
- if refractory to treatment, consider classification based on colon transit time; can measure colonic transit time with radio-opaque (Sitz) markers that are ingested and followed with a series of plain film abdominal x-rays (normal: elimination of markers within 70 h)
  1. normal = misperception of normal defecation (IBS)
  2. prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
  3. outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- combination of 1 and 3 common

Treatment (in order of increasing potency)
- dietary fibre
  - useful if mild or moderate constipation, but not if severe
  - aim for 30 g daily, increase dose slowly
- surface-acting (soften and lubricate)
  - docusate salts (likely limited efficacy based on evidence), mineral oils
- osmotic agents (effective in 2-3 d)
  - polyethylene glycol 3350, lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, i.e. milk of magnesia), lactitol (β-galactosido-sorbitol)
- cathartics/stimulants (effective in 24 h)
  - senna, bisacodyl
- enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl suppository)
- prokinetic agents (e.g. prucalopride, HT4 inhibitor)
- secretagogues: linaclotide, plecanatide (increases water secretion into the intestinal lumen)
- NHE3 (sodium-proton) inhibitors: tenapanor

Upper Gastrointestinal Bleeding

Definition
- bleeding proximal to the ligament of Treitz, see *Overview of Gastrointestinal Tract, G2* (75% of GI bleeds)
  - ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

Etiology
- above the GE junction
  - epistaxis
  - esophageal varices (10-30%)
  - esophagitis
  - esophageal cancer
  - Mallory-Weiss tear (10%)
- stomach
  - gastric ulcer (20%) (see *Peptic Ulcer Disease, G11*)
  - erosive gastritis (e.g. from EtOH or post-surgery) (20%)
  - gastric cancer
  - gastric antral vascular ectasia (rare, associated with cirrhosis and connective tissue disease)
  - Dieulafoy's lesion (very rare)
- duodenum
  - ulcer in bulb (25%)
  - aortoenteric fistula: usually only if previous aortic graft (see sidebar)

Always ask about NSAID/Aspirin® or anticoagulant therapy in GI bleed

Aortoenteric Fistula is a rare and lethal cause of GI bleed, most common in patients with a history of aortic graft surgery. Therefore, perform emergency endoscopy if suspected, emergency surgery if diagnosed
Note: The window of opportunity is narrow. Suspect if history of aortic graft, abdominal pain associated with bleeding

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding
NEJM 2013;368:11-21
Study: Prospective, unblinded, RCT, follow-up up to 45 d.
Population: 921 patients with hematemesis, bloody nasogastric aspirate, melena, or both. Exclusion criteria included massive bleed, acute coronary syndrome, stroke/ transient ischemic attack or transfusion within previous 90 d; recent trauma/ surgery; lower GI bleed.
Intervention: Patients randomized to restrictive (<70 g/L) or liberal (<90 g/L) transfusion.
Outcome: Mortality, further bleeding, adverse events.
Results: Fewer patients in the restrictive group required transfusion (51% vs. 15%; P <0.001). The hazard ratio for death for restrictive compared to liberal transfusion was 0.55; 95% CI 0.33-0.92; P=0.02. Further bleeding occurred in 10% vs. 16% (P=0.01) of patients, while adverse effects occurred in 40% vs. 48% (P=0.02) of patients in the restrictive and liberal strategies, respectively. The restrictive strategy had a better survival rate in patients with bleeding associated with cirrhosis Child-Pugh class A or B (HR: 0.30; 95% CI 0.11-0.85), but not in cirrhosis Child-Pugh class C (HR: 1.04; 95% CI 0.45-2.37) or a peptic ulcer (HR: 0.70; 95% CI 0.26-1.25).
Conclusions: Transfusing patients with an acute UGIB at Hb of <70 g/L rather than 90 g/L is associated with fewer transfusions, better survival, and fewer adverse events.

- coagulopathy (drugs, renal disease, liver disease)
- vascular malformation (Dieulafoy's lesion, arteriovenous malformation)

Clinical Features
- in order of decreasing severity of the bleed: hematochezia (brisk UGIB) > hematemesis > melena > coffee ground emesis > occult blood in stool

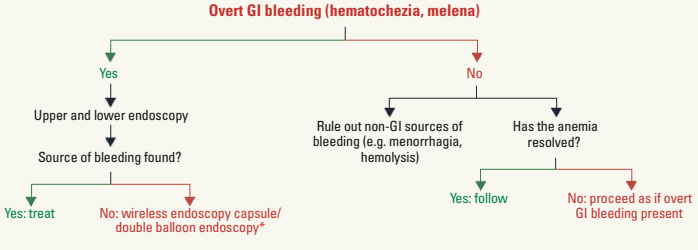
Treatment
- stabilize patient (1-2 large bore IVs, IV fluids, monitor)
- send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
- keep NPO
- consider nasogastric (NG) tube to determine upper vs. lower GI bleeding in some cases
- IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  - given to stabilize clot, not to accelerate ulcer healing
  - if given before endoscopy, decreases need for endoscopic therapeutic intervention
- for variceal bleeds, octreotide 50 µg loading dose followed by constant infusion of 50 µg/h and ABx for those with cirrhosis (reduces risk of infections)
- consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach
- H2-antagonists should not be used since they have minimal impact on rebleeding rates and need for surgery
- endoscopy (EGD): establish bleeding site + treat lesion
  - if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  - endoclips
  - Hemospray™
  - dual therapy (more than one therapeutic intervention method) is standard of care and has greater efficacy than single therapy

Forrest Prognostic Classification of Bleeding Peptic Ulcers

Forrest Class	Type of Lesion	Risk of Rebleed (%)
I	Arterial bleeding (oozing/spurting)	55-100
IIa	Visible vessel	43
IIb	Sentinel clot	22
IIc	Hematin covered flat spot	10
III	No stigmata of hemorrhage	5

Lancet 1974;2:394-397

Prognosis
- 80% stop spontaneously
- peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
- endoscopic predictors of rebleeding (Forrest classification): spurt or ooze, visible vessel, fibrin clot
- can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no high-risk predictors of rebleeding
- esophageal varices have a high rebleeding rate (55%) and mortality (29%)


Overt GI bleeding (hematochezia, melena)
Yes
No
Upper and lower endoscopy
Source of bleeding found?
Yes: treat
No: wireless endoscopy capsule/ double balloon endoscopy*
Rule out non-GI sources of bleeding (e.g. menorrhagia, hemolysis)
Has the anemia resolved?
Yes: follow
No: proceed as if overt GI bleeding present

* Wireless endoscopy capsule results help double balloon endoscopy localize source of bleeding
- Angiography if overt bleeding hemodynamically significant, estimated >0.5 cc/min
- CT enterography if wireless endoscopy capsule/double balloon endoscopy not available

Figure 9. Approach to iron deficiency anemia

Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations from the International Consensus Group
Ann Intern Med 2019;171:805-822

Pre-Endoscopic Management: In patients without cardiovascular disease, the suggested Hb threshold for blood transfusion is <80 g/L. The threshold is higher for patients with cardiovascular disease.

Endoscopic Management: Patients with acute UGIB should undergo endoscopy within 24 h of presentation. In patients with high-risk stigmata, thermocoagulation and sclerosant injection are recommended. TC-325, a hemostatic powder, can be used as a temporizing agent for actively bleeding ulcers.

Pharmacologic Management: High-dose PPI should be given for 3 d to patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy. Continued oral PPI therapy is recommended twice daily for 14 d, then once daily for a duration that depends on the nature of the bleeding lesion.

Esophageal Varices

Definition
- dilated esophageal veins connecting portal and systemic circulation

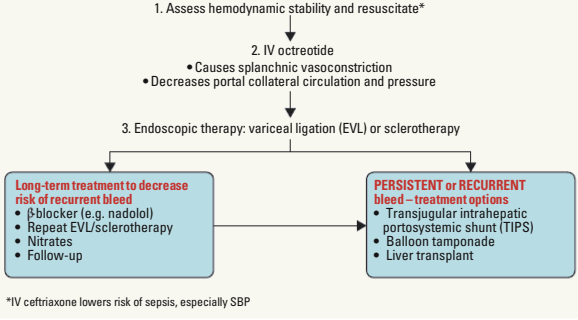
Etiology
- almost always due to portal hypertension

Clinical Features
- characteristically massive upper GI bleeding

Prognosis
- risk of bleeding: 30% in 1st yr
- risk of rebleeding: 50-70% (20% mortality at 6 wk)

Investigations
- endoscopy

Management
- empirical treatment with broad-spectrum antibiotics (such as ceftriaxone) reduces mortality in variceal bleeding and should be initiated as soon as variceal bleeding is suspected, as early administration is associated with a lower rebleeding rate and lower mortality


1. Assess hemodynamic stability and resuscitate*
2. IV octreotide
• Causes splanchnic vasoconstriction
• Decreases portal collateral circulation and pressure
3. Endoscopic therapy: variceal ligation (EVL) or sclerotherapy
Long-term treatment to decrease risk of recurrent bleed
• β-blocker (e.g. nadolol)
• Repeat EVL/sclerotherapy
• Nitrates
• Follow-up
PERSISTENT or RECURRENT bleed – treatment options
• Transjugular intrahepatic portosystemic shunt (TIPS)
• Balloon tamponade
• Liver transplant
*IV ceftriaxone lowers risk of sepsis, especially SBP

If varices isolated to stomach, think of splenic vein thrombosis

Gastric varices best treated by endoscopic injection of cyanoacetate ("crazy glue")

Figure 10. Management of bleeding esophageal varices

Mallory-Weiss Tear

Definition
- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

Etiology
- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia often present

Clinical Features
- hematemesis ± melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

Management
- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection ± clips or surgical repair

Lower Gastrointestinal Bleeding

Definition
- bleeding distal to ligament of Treitz

Etiology
- **anatomic**
  - diverticular
- **vascular**
  - angiodysplasia (small vascular malformations of the gut)
  - anorectal (hemorrhoids, fissures)
- **inflammatory**
  - infection
  - inflammatory bowel disease
  - colitis (ulcerative, infectious, radiation, ischemic) (see *Ulcerative Colitis, G25*)
- **neoplasm**
- polyp(s)
- post-polypectomy
- cancer

Lower GI Bleed

CHAND
Colitis (radiation, infectious, ischemic, IBD (UC > CD))
Hemorrhoids/fissure
Angiodysplasia
Neoplasm
Diverticular disease

Clinical Features
- hematochezia
- anemia
- occult blood in stool (no visible blood, detected via FIT)
- occasionally melena due to slow small bowel or right-colonic course

Treatment
- if blood per rectum with hemodynamic instability, stabilize patient (1-2 large bore IVs, IV fluids, monitor) and rule out upper GI source with endoscopy (EGD)
- send blood for CBC, cross and type, INR/PTT, electrolytes, BUN, Cr, LFTs
- initial examination of choice is colonoscopy to determine source of the bleeding

- if bleeding is severe or ongoing, consider radionuclide imaging or angiography (see Medical Imaging, MI16)
- treat underlying cause
  - majority of cases will stop bleeding spontaneously

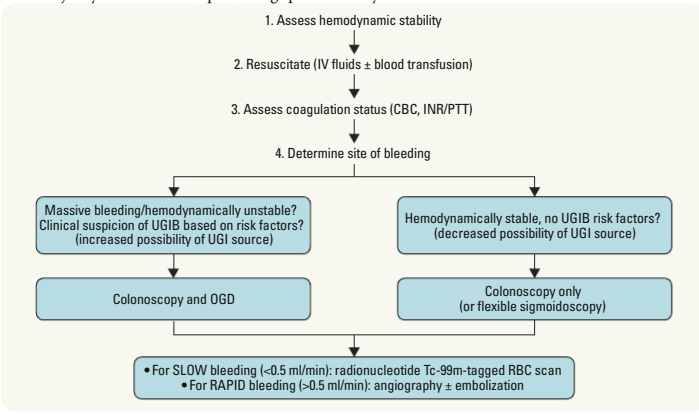


Figure 11. Approach to hematochezia

Always exclude upper GI lesion before localizing the site of the bleeding to the lower GI tract

Diverticular Bleeding

Etiology
- herniation of diverticula exposes vasa recta, increasing susceptibility to disruption
- bleeding most common from the right colon (thinner walled), although diverticula often develop throughout colon

Clinical Features
- painless hematochezia, acute onset
- stool can range from bright red to dark maroon; gelatinous clots often mixed in
- 80% of diverticular bleeding resolves spontaneously without intervention

Management
- if colonoscopy identifies source (rare), hemostatic therapy can be applied
- if ongoing, can consider embolization or surgery

Infectious Colitis

Etiology
- variety of pathogens; often due to *Campylobacter, Entamoeba histolytica, Salmonella, E. coli, Shigella*
- consider travel history, food exposures

Clinical Features
- bloody diarrhea, fever, abdominal pain

Management
- stool cultures to determine pathogen and guide management
- see *Acute Diarrhea, G15*

Colorectal Carcinoma

- see General Surgery and Thoracic Surgery, GS43

Colorectal Polyps

- see General Surgery and Thoracic Surgery, GS41

Familial Colon Cancer Syndromes

- see General Surgery and Thoracic Surgery, GS42

Benign Anorectal Disease

- see General Surgery and Thoracic Surgery, GS47

Liver

Investigations of Hepatobiliary Disease

A. Tests of Liver Function

Table 17. Liver Function Tests

Test	What Do Levels Correlate With?	Increased by	How to Interpret
Prothrombin Time (PT or INR)	Hepatic protein synthesis All coagulation factors except VIII	Increased by: Hepatocellular dysfunction Vitamin K deficiency (due to malnutrition, malabsorption, etc.)	PT/INR will promptly correct if vitamin K is administered, so increased PT/INR in absence of vitamin K deficiency is a reliable marker of hepatocellular dysfunction
Serum Albumin	Hepatic protein synthesis (and other causes listed in next column)	Decreased by: Hepatocellular dysfunction Malnutrition Renal or GI losses Significant inflammation Malignancy	Rule out potential causes other than hepatocellular dysfunction
Serum Direct Bilirubin*	Hepatic excretion from hepatocyte to biliary system	Increased by: Liver dysfunction	Conjugation is preserved even in end stage liver failure, thus increased direct bilirubin indicates liver dysfunction

*Serum Bilirubin
• canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
• direct bilirubin = conjugated; indirect bilirubin = unconjugated

B. Tests of Liver Injury

Table 18. Liver Enzyme Profile

Profile	Liver Enzyme Change	Notes
Hepatocellular	↑ AST ↑ ALT	AST from multiple sources (especially muscle) ALT more specific to liver Elevation of both highly suggestive of liver injury
Cholestatic	↑ ALP ↑ GGT	Cholestasis = stasis of bile flow If ALP is elevated alone, rule out bone disease by fractionating ALP and/or checking GGT If ALP elevation out of proportion to ALT/AST elevation, consider: • Obstruction of common bile duct (e.g. extraluminal = pancreatic cancer, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths) • Predominant rise in hepatocellular enzyme possible in acute biliary obstruction secondary to a stone due to the sudden impairment in bile flow and because ALP is an inducible enzyme which takes time to rise • Destruction of microscopic ducts (e.g. PBC) • Bile acid transporter defects (e.g. drugs, intrahepatic cholestasis of pregnancy) • Infiltration of the liver (e.g. liver metastases, lymphoma, granulomas, amyloid)

Acute Viral Hepatitis (General)

Definition
- viral hepatitis lasting <6 mo

Clinical Features
- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
  - N/V, anorexia, headaches, fatigue, myalgia, low-grade fever, arthralgia, and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
  - pale stools and dark urine 1-5 d prior to icteric phase
  - hepatomegaly and RUQ pain
  - splenomegaly and cervical lymphadenopathy (10-20% of cases)

Quick Reference Diagnostic Tests for Common Liver Conditions

Disease	Diagnostic Tests
Viral Hepatitis	Anti-HAV IgM, HBsAg, anti-HCV
Autoimmune Hepatitis	ANA, SMA, LKM, IgG levels
Wilson's Disease	Ceruloplasmin, liver biopsy
Hereditary Hemochromatosis	Iron saturation, ferritin, HFE genetic testing
α1-Antitrypsin Deficiency	α1-antitrypsin levels/ genotyping, liver biopsy
Drug-induced Liver Injury	Careful medication history, liver biopsy
NAFLD/Nonalcoholic Steatohepatitis (NASH)	U/S, metabolic testing, liver biopsy

ANA = anti-nuclear antibody; SMA = smooth muscle antibody; LKM = liver-kidney microsomal-1 antibody; HFE = hemochromatosis gene

DDx for Hepatomegaly
- Congestive (right heart failure, Budd-Chiari syndrome)
- Infiltrative
- Malignant (primary, secondary, lymphoproliferative, leukemia)
- Benign (fatty liver, cysts, hemochromatosis, extramedullary hematopoiesis, amyloid)
- Proliferative
- Infectious (viral, tuberculosis, abscess, echinococcus)
- Inflammatory (granulomas (sarcoid), histiocytosis X)

All clotting factors except factor VIII and von Willebrand factor are exclusively synthesized in the liver. Factor VIII is also produced in the endothelium. In cirrhosis, risk of bleeding does not correlate closely with elevations in INR/ PTT since so many of the proteins in the coagulation cascade are affected

ALT > AST = most causes of hepatitis
AST > ALT = alcoholic liver disease or other causes of hepatitis (i.e. non-alcoholic liver disease) that have progressed to advanced cirrhosis

Serum Transaminases >1000 due to
- Viral hepatitis
- Drugs/toxins
- Autoimmune hepatitis
- Hepatic ischemia
- Less often, common bile duct stone

Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP minimally elevated
- viral serology, particularly IgM antibody directed to the virus

Treatment
- supportive (hydration, diet)
- usually resolves spontaneously, but if severe HBV infection, treatment with antiviral agent such as tenofovir or entecavir can be considered; in acute hepatitis C, antiviral treatment should be considered (see *Hepatitis C Virus, G34*)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin (>340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia

Complications
- cholestasis (most commonly associated with HAV infection)
- hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

Hepatitis A Virus

- RNA virus
- fecal-oral transmission; incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice, hepatomegaly
- can cause ALF and subsequent death (<1-5%)
- can relapse (rarely), but never becomes chronic
- treatment is supportive (no specific treatments available, disease is often self-limiting)
- preventable by vaccination

Hepatitis B Virus

Table 19. Hepatitis B Serology

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	Liver Enzymes
Acute HBV	+	–	+	–	IgM	
Chronic (HBe-Ag positive) HBV (generally high HBV- DNA)	+	–	+	–	IgG	ALT, AST may or may not be elevated
Chronic (HBe-Ag negative) HBV (generally low HBV- DNA)	+	–	–	+	IgG	ALT, AST may or may not be elevated
Resolved Infection	–	±	–	±	IgG	
Immunization	–	+	–	–	–	

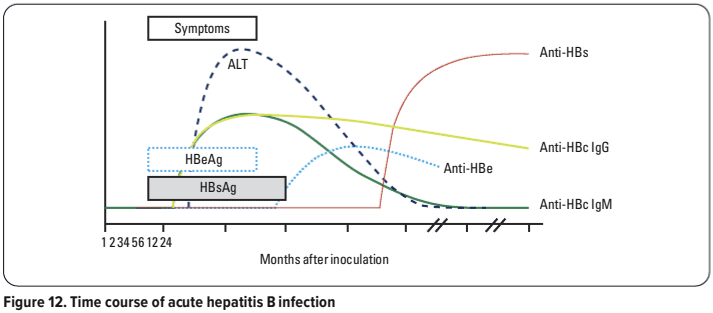


Figure 12. Time course of acute hepatitis B infection

Alcoholic Hepatitis: history of chronic EtOH use (possibly with recent increased consumption, although often patient may have stopped drinking in the days-weeks prior to presentation due to symptoms), RUQ abdominal pain, AST/ALT >2, AST usually <300, low grade fever, mildly elevated WBC

Major Sources of ALP
Hepatobiliary tree
Bone
Placenta
Intestine

DDx for Hepatitis
Viral infection
Alcohol
Drugs
Immune-mediated
Toxins

Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury

Risk of HCC in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis, and serum HBV-DNA
Risk of HCC in HCV increases only after cirrhosis develops

HCV (and HBV) treatment lowers the risk of HCC

Risk Factors for Progression
EtOH
HIV coinfection
Old age at diagnosis

Epidemiology

- 4 phases of chronic hepatitis B: not all carriers will go through all 4 phases, but all carriers will have positive HBsAg
    1. **immune tolerance**: extremely high HBV-DNA (>20000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or 'incubation period' in adult with newly-acquired HBV)
    2. **immune clearance (or immunoactive):** HBV-DNA levels (>20000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or HCC); likely to benefit from treatment
    3. **inactive carrier (immune control):** lower HBV-DNA (<2000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
    4. **HBeAg-negative chronic hepatitis (immune escape) ("core or precore mutant"):** elevated HBV-DNA (>2000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or HCC); likely to benefit from treatment

Treatment

- counselling: 40% of men and 10% of women with perinatal infection without treatment will die from HBV-related complications
- HCC screening with U/S q6 mo, especially if high serum HBV-DNA levels, cirrhosis, men, (ages >40 in Asian men, >50 in Asian women, and >20 in African descent)
- contexts to consider pharmacological therapy:
    1. HBeAg positive and HBV-DNA >20000 IU/mL and elevated ALT
    2. HBeAg negative and HBV-DNA >2000 IU/mL and elevated ALT with or without stage ≥2 fibrosis on liver biopsy
    3. to prevent flare when placed on immunosuppressive therapy such as prednisone, chemotherapy, biologics, etc.
- treatment goal: reduce serum HBV-DNA to undetectable level
    - prolonged immune-mediated damage leads to higher risk of liver fibrosis
- treatment options: tenofovir, entecavir, lamivudine (not preferred due to high rate of developing resistance)
- vaccinate against HAV if serology negative (to prevent further liver damage)
- follow blood and sexual precautions
- vaccinate household contacts

Hepatitis D Virus

- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with HBV; causes more aggressive disease than HBV alone
- coinfection: acquire HDV and HBV at the same time
- superinfection: new acquisition of HDV on a background of chronic HBV infection (e.g. injection drug users)
- HDV can present as ALF and/or accelerate progression to cirrhosis
- treatment: low-dose interferon (20% response) and liver transplant for end-stage disease

Hepatitis C Virus

- RNA virus (7 genotypes; genotype 1 is most common in North America)
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factor: injection drug use
- other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
- acute hepatitis C occurs 2-6 mo after transmission
    - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage
    - almost 30% of cases of acute hepatitis C are cleared spontaneously without therapy

Diagnosis

- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- normal hepatocellular enzymes does not rule out active disease or presence of advanced fibrosis
- abdominal U/S and transient elastography (FibroScan®) to assess the staging of the disease and the degree of fibrosis

In acute hepatitis B, HDV coinfection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis

Causes of Elevated Serum Transaminases in Chronic Hepatitis B
Active hepatitis (either immune clearance phase in HBeAg-positive individuals or HBeAg-negative active hepatitis)
Reactivation (e.g. due to immunosuppression)
Hepatitis D
Other liver insult (fatty liver, EtOH, drugs, hepatitis A)

Risk Factors for Contracting Hepatitis B
Infants born to a hepatitis B-infected parent (maternal or paternal)
Unprotected sexual intercourse (especially if multiple partners)
Needle sharing (e.g. injection drug users)
Travel to endemic regions
Exposure to human blood, semen, and other bodily fluids

Clinical Features of Hepatitis B
Many patients are asymptomatic, both in the acute and chronic phases
Acute hepatitis can manifest as jaundice, nausea, arthritis, or constitutional symptoms
Patients with chronic hepatitis can be asymptomatic, experience exacerbations, develop extrahepatic complications (e.g. glomerular disease), or develop cirrhosis

Treatment

- blood-borne precautions; vaccinate for hepatitis A and B if serology negative; avoid EtOH
- clearest indication for treatment is in subgroups likely to develop clinically significant liver disease, i.e. persistently elevated transaminases, liver biopsy showing moderate-advanced fibrosis/cirrhosis, and at least moderately severe necrosis/inflammation
  - now that a safe, effective cure is available, the risk/benefit ratio favours treating everyone with chronic hepatitis C
- choice and duration of treatment depends mostly on whether patient is cirrhotic (and if so, whether decompensated or not), prior treatment history, and possibly genotype (but less so with availability of pan-genotypic therapies)
- direct acting antiviral (DAA) tablets (Maviret®, a combination of glecaprevir and pibrentasvir, and Epclusa®, a combination of velpatasvir and sofosbuvir) are the most commonly used
- other oral interferon-free regimens (for all genotypes) (e.g. sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir+dasabuvir, or elbasvir/grazoprevir, and sofosbuvir/velpatasvir) are also available but used less frequently
- it is important to check for hepatitis B prior to therapy as direct acting antivirals may lead to reactivation of hepatitis

Prognosis

- 80% of acute hepatitis C cases become chronic (of these, 20% evolve to cirrhosis within 20 years of exposure)
- risk of HCC increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

Table 20. Characteristics of the Viral Hepatitides

	HAV	HBV	HCV	HDV	HEV	CMV	EBV	Yellow Fever
Virus Family	*Picomaviridae*	*Hepadnaviridae*	*Flaviviridae*	*Deltaviridae*	*Caliciviridae*	*Herpesviridae*	*Herpesviridae*	*Flavivirus*
Genome	RNA	DNA	RNA	RNA	RNA	DNA	RNA	RNA
Envelope	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Transmission	Fecal-oral	Parenteral/sexual or equivalent Vertical	Parenteral/sexual (transfusion, IV drug user, sexual (<HBV)) 40% have no known risk factors	Non-parenteral (close contact in endemic areas) Parenteral (blood products, IV drug user) —sexual transmission is inefficient	Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan)	Close contacts, most body fluids	Saliva-oral	Vector (mosquito)
Incubation	4-6 wk	6 wk-6 mo	2-26 wk	3-13 wk	2-8 wk	20-60 d	30-50 d	3-6 d
Onset	Usually abrupt	Usually insidious	Insidious	Usually abrupt	Usually abrupt	Variable	Variable	Usually abrupt
Communicability	2-3 wk in late incubation to early clinical phase Acute hepatitis in most adults, 10% of children	HBsAg+ state highly communicable Increased during third trimester or early post-partum	Communicable prior to overt symptoms and throughout chronic illness	Infectious only in presence of HBV (HBsAg required for replication)	Unknown	Variable – dormant or persistent	Highly communicable during year after primary infection but never zero	Variable, vector-dependent
Chronicity	None, although can relapse	5% adults, 90% infants	80%, 20% of which develop cirrhosis	5%	None	Common; latent	Common; latent	Infection confers lifelong immunity
Serology	Anti-HAV (IgM)	**See** *Table 19, G33*	HCV-RNA Anti-HCV (IgG/IgM)	HBsAg Anti-HDV (IgG/IgM)	Anti-HEV (IgG/IgM)	Anti- CMV (IgM/IgG)	Monospot; anti-EBV IgM/IgG, EBV-DNA quantitation	Anti-YF (IgM/IgG)
Vaccine	Havrix®, 2 doses q6 mo, combined with Twinrix® at 0, 7, and 21 d	Recombivax® HBTM, ages 11-15, 2 doses q6 mo	No	No	No	No	No	YF-VAX®, 1 dose booster q10 yr
Management	General hygiene Treat close contacts (anti-HAV Ig) Prophylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune	Prevention: HBV vaccine and/or hepatitis B Ig (HBIg) for needlestick, sexual contact, infants of infected mothers (unless already immune) Rx: oral antivirals vs. interferon if indications met	Prevention: no vaccine Rx: interferon + ribavirin ± protease inhibitor; although all oral antiviral (IFN-free) therapies now available are highly efficacious	Prevention: HBV vaccine	Prevention: general hygiene, no vaccine	In high-risk transplant patients: CMV Ig and antivirals (ganciclovir, valganciclovir)	Supportive treatment post-infection	Prevention: vaccine Supportive treatment post infection
Acute Mortality	0.1-0.3%	0.5-2%	1%	2-20% coinfection with HBV, 30% superinfection Predisposes HBV carriers to more severe hepatitis and faster progression to cirrhosis	1-2% overall, 10-20% in pregnancy	Rare in immunocompetent adults	Rare	20-60% in developing countries
Oncogenicity	No	Yes	Yes	Yes	No	No	Yes	No
Complications	Can cause ALF and subsequent death (<1-5%)	HCC secondary to cirrhosis, serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda	HCC in 2-5% of cirrhosis per yr, cryoglobulinemia, B-cell non-Hodgkin lymphoma	Leukocytoclastic vasculitis, membranous glomerulonephropathy	Mild, except in third trimester (10-20% ALF)	5% of newborns with multiple handicaps Immunocompromised patients at risk of CMV-induced hepatitis, retinitis, colitis, esophagitis, pneumonitis	Associated with Burkitt's lymphoma and nasopharyngeal carcinoma (rare in Western world)	Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates

Autoimmune Liver Disease

- diagnosis of exclusion: rule out viruses, drugs/EtOH, metabolic, or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrahepatic manifestations
  - sicca, Raynaud's, thyroiditis, Sjögren's, arthralgias
  - hypergammaglobulinemia (particularly elevated IgG)
  - typical auto-antibodies: ANA and/or anti-smooth muscle antibody
  - infrequently may see anti-LKM elevation (liver kidney microsome), especially in children
  - can have false positive viral serology (especially anti-HCV)
  - biopsy – periportal (zone 1) and interface inflammation and necrosis
- treatment: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

Drug-Induced Liver Disease

Table 21. Classification of Hepatotoxins

	Predictable	Idiosyncratic
Example	Acetaminophen, CCl4	Phenytoin, INH
Dose-Dependence	Usual	Unusual
Latent Period	Hours-days	Weeks-months
Host Factors	Not important	Very important

Hy's Law: drug-induced hepatocellular jaundice indicates a mortality of at least 10%

- many different patterns of liver injury (i.e. hepatocellular, cholestatic, mixed, granulomatous, ALF) can be seen in drug-induced liver injury and thus this requires a high index of suspicion
- see: LiverTox for Information regarding drug-specific risks and patterns of hepatotoxicity (http://livertox.nih.gov)

Specific Drugs

- acetaminophen
  - metabolized by hepatic cytochrome P450 system
  - can cause ALF (transaminases >1000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy individuals, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite (NAPQI (n-acetyl-p-benzoquinone imine)) is formed → covalently binds to hepatocyte membrane
  - presentation
    - first 24 h: nausea and vomiting (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with ALF or resolution
    - note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy
    - gastric lavage/emesis (if <2 h after ingestion)
    - oral activated charcoal
    - N-acetylcysteine (NAC – Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given regardless of time of ingestion)
      - promotes hepatic glutathione regeneration
    - no recorded fatal outcomes if NAC given before increase in transaminases
    - NAC use should be determined by the Rumack-Matthew nomogram or if unclear, time of ingestion
- antimicrobials are the most common class of causative agent (e.g. amoxicillin-clavulanate, isoniazid, nitrofurantoin, sulfamethoxazole-trimethoprim)
- chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus, and eosinophilia
- Isoniazid (INH)
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age
- Methotrexate (MTX)
  - causes fibrosis/cirrhosis; increased risk in the presence of obesity, DM, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
- others: azoles, statins, methyldopa, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines
- herbs: khat, chaparral, Chinese herbs (e.g. germander, comfrey, bush tea). Weight loss supplements (containing green tea extract) have been associated with cases of acute liver failure. Body-building supplements have been associated with prolonged cholestatic jaundice)

Wilson's Disease

Definition
- autosomal recessive defect in copper elimination (gene *ATP7B*)

Etiology
- decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin
- worldwide incidence: 1 in 40000

Clinical Features
- liver: acute hepatitis, ALF, chronic active hepatitis, cirrhosis, low-risk of HCC
- eyes: Kayser-Fleischer rings (copper deposits in Descemet's membrane); more common in patients with CNS involvement, present in only 50% of isolated liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi's syndrome (proximal tubule transport defects) and stones
- blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
- joints: arthritis, bone demineralization, calcifications

Clinical Manifestations of Wilson's Disease

ABCD
Asterixis
Basal ganglia degeneration: suspect if parkinsonian features in the young
Ceruloplasmin decreases
Cirrhosis
Corneal deposits (Kayser-Fleischer ring)
Copper
Dementia

Investigations
- suspect if increased liver enzymes with clinical manifestations at young age (<40); especially combination of liver disease with dystonia, psychiatric symptoms
- screening tests
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion (measure 24-hour urine copper)
- gold standard
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible
- first-degree relatives should also be considered for screening

Treatment
- 4 drugs available
  1. penicillamine: chelates copper, but poorly tolerated
  2. trientine: chelates copper
  3. zinc: impairs copper excretion in stool and decreases copper absorption from gut. Often used as maintenance therapy or in neurologic presentations
  4. tetrathiomolybdate: preferred if neurological involvement
- hepatic presentations are best treated with a trientine + zinc combination
- liver transplant in severe cases of liver failure

Hemochromatosis

Definition
- excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body iron stores increased to 20-40 g (normal 1 g)

Etiology
- primary (hereditary) hemochromatosis
  - usually related to HFE mutation (see Epidemiology below)
  - decreased hepcidin production results in increased GI absorption and tissue iron deposition despite adequate iron stores
- secondary hemochromatosis
  - parenteral iron overload (e.g. transfusions, hemodialysis, parenteral iron injections)
  - excessive oral iron intake (e.g. dietary iron overload)
  - other liver diseases (e.g. EtOH, NAFLD, viral hepatitis)
  - iron-loading anemias (hemolytic, sideroblastic, aplastic, thalassemia major)
  - ineffective erythropoiesis

Epidemiology
- classic hereditary hemochromatosis most common in Northern European descent
- mainly caused by mutations in the *HFE* gene (e.g. C282Y/C282Y, C282Y/H63D), which has a homozygous genetic prevalence of 1/400
  - C282Y/H63D only potentially causative as compound heterozygote
- very rare non-HFE mutations also exist (e.g. ferroportin, hemojuvelin, hepcidin, aceruloplasminemia)

Hemochromatosis Clinical Features

ABCDH
Arthralgia
Bronze skin
Cardiomyopathy, cirrhosis of liver
Diabetes (pancreatic damage)
Hypogonadism (anterior pituitary damage)

Clinical Features
- usually presents with trivial elevation in serum transaminases although often picked up incidentally when iron studies noted to be elevated
- liver: cirrhosis (less common nowadays due to earlier detection), HCC (200x increased risk)
- pancreas: DM, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: diastolic dysfunction and arrhythmias in early stages with dilated cardiomyopathy in later stages
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint, but especially metacarpophalangeal joints), chondrocalcinosis

Ferritin may never normalize if other causes of high ferritin present (e.g. fatty liver from metabolic syndrome or EtOH)

Investigations
- screening for individuals with clinical features and/or family history (25% chance of sibling having the disease)
  - transferrin saturation (free Fe^{2+}/total iron binding capacity (TIBC)) >45%
  - serum ferritin >400 ng/mL
  - *HFE* gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
- MRI (often used instead of a liver biopsy)
  - non-invasive approach to assess iron overload
  - most sensitive and specific modality in the diagnosis of hemochromatosis
  - serum ferritin >1000 ng/mL or symptoms of organ injury (e.g. elevated LFTs, symptoms of heart failure)
  - can be used to follow treatment by phlebotomies
- liver biopsy (generally used to detect cirrhosis or if potential for other causes of liver disease)
  - markers of advanced fibrosis: if any of the following are present at the time of diagnosis → ages >40, elevated liver enzymes, or ferritin >1000 ng/mL
  - considered if compound heterozygote and potential other cause of liver injury (e.g. NAFLD, excess EtOH, hepatitis)
  - if C282Y/C282Y and no markers of advanced fibrosis, then biopsy generally not needed
- HCC screening if cirrhosis

Treatment
- phlebotomy: weekly or q2 wk then lifelong maintenance phlebotomies q2-6 mo, generally aiming for ferritin of 50-100 ng/mL
- chelation therapy such as deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

Prognosis
- normal life expectancy if treated before the development of cirrhosis or DM

Alcoholic Liver Disease

Definition
- spectrum of diseases, ranging from:
  - fatty liver (common amongst individuals with EtOH use disorder): reversible if EtOH stopped
  - alcoholic hepatitis (35% of individuals with EtOH use disorder): usually reversible if EtOH stopped
  - cirrhosis (10-15% of individuals with EtOH use disorder): irreversible

Standard Drink Equivalent
1 standard drink = 14 g EtOH
= 12 oz beer (5% alcohol)
= 5 oz wine (12-17%)
= 3 oz fortified wine (17-22%)
= 1.5 oz liquor (40%)
Tip: percentage EtOH multiplied by oz in 1 standard drink roughly equals 60

Pathophysiology
- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde
  - reduces NAD+ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- EtOH increases gut permeability leading to increased bacterial translocation
- EtOH metabolism causes:
  - relative hypoxia in liver zone III (near central veins; poorly oxygenated) > zone I (around portal tracts, where oxygenated blood enters)
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

Biopsy + Histology of Alcoholic Hepatitis (triad)

Hepatocyte necrosis with surrounding inflammation in zone III

Mallory bodies (intracellular eosinophilic aggregates of cytokeratins)

Chicken-wire fibrosis (network of intralobular connective tissue surrounding cells and venules)

Clinical Features
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10-20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of EtOH consumed above threshold
- clinical findings do not accurately predict type of liver involvement
- fatty liver
  - mildly tender hepatomegaly; jaundice rare
  - mildly increased transaminases <5x normal
- alcoholic hepatitis
  - variable severity: mild to fatal liver failure
  - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice, and mildly elevated INR)
  - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased WBC count – mimics right lower lobe pneumonia and cholecystitis

Investigations
- blood tests are non-specific, but in general
  - AST:ALT >2:1 (both usually <300)
  - CBC: increased mean corpuscular volume (MCV), increased WBC often seen with alcoholic hepatitis but not necessarily in other alcohol-related liver injury
  - increased GGT

Treatment
- alcohol cessation (see Psychiatry, PS28)
  - Alcoholics Anonymous (or similar programs), disulfiram, naltrexone, acamprosate
- multivitamin supplements (especially thiamine)
- caution with drugs metabolized by the liver
- prednisolone if severe alcoholic hepatitis based on Maddrey's discriminant function or Model for End-Stage Liver Disease (MELD) score as described in Prognosis
  - pentoxifylline less used since most definitive trial did not demonstrate efficacy

Prognosis
- Maddrey's discriminant function (based on PT and bilirubin) and MELD predict mortality and guide treatment (consideration of corticosteroids for severe disease based on Maddrey ≥32 or MELD ≥21)
- bilirubin response at day 7 of corticosteroids (Lille model) also factors into prognosis and decision on whether to continue full course of corticosteroids if started
- fatty liver: complete resolution with cessation of EtOH intake
- alcoholic hepatitis mortality
  - immediate: 30%-60% in the first 6 mo if severe
  - with continued EtOH: 70% in 5 yr
  - with cessation: 30% in 5 yr

GI Complications of Alcohol Use

Esophagus
Mallory-Weiss tear
Esophageal varices (secondary to portal hypertension)

Stomach
Alcoholic gastritis

Pancreas
Acute pancreatitis
Chronic pancreatitis

Liver
Alcoholic hepatitis
Fatty liver
Cirrhosis
Hepatic encephalopathy
Portal hypertension
Ascites
HCC

Non-Alcoholic Fatty Liver Disease

Definition
- spectrum of disorders characterized by macrovesicular hepatic steatosis, sometimes with inflammation and/or fibrosis
- most common cause of liver disease in North America

Etiology
- pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- histological changes indistinguishable from those of alcoholic hepatitis despite negligible history of EtOH consumption

Risk Factors
- component of the metabolic syndrome along with obesity, T2DM, HTN, hypertriglyceridemia
- other less common causes such as medications (e.g. tamoxifen, corticosteroids, MTX), Wilson's, TPN, rapid weight loss, and others

Clinical Features
- often asymptomatic
- may present with fatigue, malaise, and vague RUQ discomfort

Investigations
- elevated serum AST, ALT ± ALP; AST/ALT <1
- presents as echogenic liver texture on U/S
- non-invasive testing of fibrosis: FIB4, NAFLD fibrosis score, FibroTest™, FibroScan®
- liver biopsy cannot distinguish fatty liver from alcoholic vs. non-alcoholic, but considered when investigating alternative etiologies or assessing for level of fibrosis

Treatment
- mainstay is gradual weight loss (0.5-1 kg/wk) as rapid weight loss can worsen liver disease
  - ideally, aim to lose at least 7-10% of body weight
- evidence for the use of pharmacologic agents such as pioglitazone and liraglutide, but potential benefits must be balanced with associated adverse effects (e.g. weight gain and CHF with pioglitazone)
- some evidence for vitamin E (800 IU daily) if there is hepatic inflammation in non-diabetic, non-cirrhotic patients
- some evidence for benefits of coffee drinking (3 cups/d) and vitamin D
- consideration for bariatric surgery
- GLP-1 analogues (e.g. semaglutide) do not appear to directly improve liver inflammation in NAFLD, but may indirectly help through promotion of weight loss

Prognosis
- main causes of death, particularly in non-cirrhotic group, are cardiovascular disease and malignancy
- better prognosis than alcoholic hepatitis
  - <25% progress to cirrhosis over a 7-10 yr period
- risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
- other clinical indicators of unfavourable prognosis: obesity, T2DM, age, metabolic syndrome, higher levels of fibrosis

Acute Liver Failure (formerly Fulminant Hepatic Failure)

Definition
- severe decline in liver function characterized by coagulation abnormality (INR >1.5) and encephalopathy
- in setting of previously normal liver
- rapid (<26 wk duration)

Figure 13. Progression of liver dysfunction based on liver function tests – the "W"

Etiology
- drugs (especially acetaminophen), hepatitis B (measure anti-HBc, IgM fraction because sometimes HBV-DNA and even HBsAg rapidly become negative), hepatitis A, hepatitis C (rare), ischemic, autoimmune hepatitis, Wilson disease, idiopathic

Treatment
- correct hypoglycemia, monitor level of consciousness, prevent GI bleed with PPI, monitor for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value of biopsy is to exclude chronic disease, less helpful for prognosis
- liver transplant (King's College criteria can be used as prognostic indicator): consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), ages <10 or >40, cause is drug or unknown, bilirubin >300 µmol/L, INR >3.5, creatinine >200 µmol/L

Cirrhosis

Definition
- liver damage characterized by diffuse distortion of the basic architecture with fibrosis and formation of regenerative nodules
- biopsy gold standard for diagnosis
- compensated cirrhosis = absence of complications, can last for 10-20 yr with almost normal life expectancy
- decompensated cirrhosis = development of complications such as ascites (most common), variceal bleeding, encephalopathy

Etiology
- fatty liver (alcoholic or NAFLD)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- drugs (e.g. chronic MTX or amiodarone use)
- hereditary hemochromatosis
- PBC
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- cryptogenic (i.e. no identifiable cause, although many of these patients may represent "burnt-out non-alcoholic steatohepatitis (NASH)")
- rare: Wilson's disease, Gaucher's disease, α1-antitrypsin deficiency

MELD-Na (Model for End-Stage Liver Disease)
Predicts 3 mo survival and used to stratify patients on transplant list
Based on creatinine, INR, total bilirubin, and serum sodium concentration

MELD 3.0
Updated score that includes new variables such as female sex and serum albumin

Investigations

- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive
- blood work
  - fall in platelet count <150 is the earliest finding
  - in late stages of cirrhosis, rise in INR, fall in albumin, rise in bilirubin
  - elevated bilirubin is usually seen in more advanced disease or in the setting of a concurrent insult
  - in very advanced cirrhosis (pre-terminal event), may also see hypoglycemia but this is more often a feature seen in severe ALF
- FibroTest™: combination of various clinical and biochemical markers that can predict degree of fibrosis
- imaging
  - U/S is the primary imaging modality but only finds advanced cirrhosis
  - CT to look for varices, nodular liver texture, splenomegaly, ascites
  - transient elastography (FibroScan®): non-invasive tool using elastography for measuring liver compliance (variable availability)
    - rapidly replacing liver biopsy to determine extent of liver fibrosis and make the diagnosis of cirrhosis
- gastroscopy: varices or portal hypertensive gastropathy

Treatment

- treat underlying disorder
- decrease insults (e.g. EtOH cessation, hepatotoxic drugs, immunize for hepatitis A and B if non-immune)
- follow patient for complications (esophageal varices, ascites, HCC)
- prognosis: Child-Pugh Score and MELD score
- liver transplantation for end-stage disease; use MELD score (e.g. MELD ≥15)

Table 22. Child-Pugh Score and Interpretation

Classification	1	2	3
Serum bilirubin (μmol/L)	<34	34-51	>51
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7-2.3	>2.3
Presence of ascites	Absent	Controllable	Refractory
Encephalopathy	Absent	Minimal	Severe
Interpretation			
Points	Class	Life Expectancy	Perioperative Mortality
5-6	A	15-50 yr	10%
7-9	B	Candidate for transplant	30%
10-15	C	1-3 mo	82%

Score: 5-6 (Child's A), 7-9 (Child's B), 10-15 (Child's C)
*Note: Child's classification is rarely used for shunting (TIPS or other surgical shunts), but is still useful to quantitate the severity of cirrhosis

Complications

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR
  - relationship of INR to bleeding tendency is controversial; some patients may be hypocoagulable, others may be hypercoagulable
- variceal bleeds
  - 1/2 of patients with cirrhosis have gastroesophageal varices and 1/3 of these develop hemorrhage with an overall mortality of >30%
  - HVPG ≥10 mmHg is the strongest predictor of variceal development
  - treatment: resuscitation, antibiotic prophylaxis, vasoactive drugs (e.g. octreotide IV) combined with endoscopic band ligation or sclerotherapy, TIPS
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to overdiuresis)
    - acute tubular necrosis
    - HRS
      - type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
    - HRS can occur at any time in severe liver disease, especially after:
      - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
      - GI bleed
      - sepsis

Cirrhosis Complications

VARICES
Varices
Ascites/Anemia
Renal failure (HRS)
Infection
Coagulopathy
Encephalopathy
Sepsis

Usual causes of death in cirrhosis: renal failure (hepatorenal syndrome), sepsis, GI bleed, or HCC

Hepatorenal Syndrome vs. Pre-Renal Failure – Difficult to Differentiate
Similar blood and urine findings
Urine sodium: very low in hepatorenal; low in pre-renal
IV fluid challenge: giving volume expanders improves pre-renal failure, but not HRS

Hepatopulmonary Syndrome

Clinical Triad
Liver disease
Increased alveolar-arterial gradient while breathing room air
Evidence for intrapulmonary vascular abnormalities

Fibrosis may regress and disappear if cause of liver injury is treated or resolves

- treatment for HRS (generally unsuccessful at improving long-term survival)
  - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
  - definitive treatment is liver transplant

- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though may be due to other chronic liver diseases, such as non-cirrhotic portal HTN
  - thought to arise from:
    - ventilation-perfusion mismatch (intrapulmonary shunting and limitation of oxygen diffusion)
    - failure of damaged liver to clear circulating pulmonary vasodilators and/or increased production of vasodilators by liver
  - clinical features
    - hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency), and orthodeoxia (desaturation in the upright position, improved by recumbency)
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation

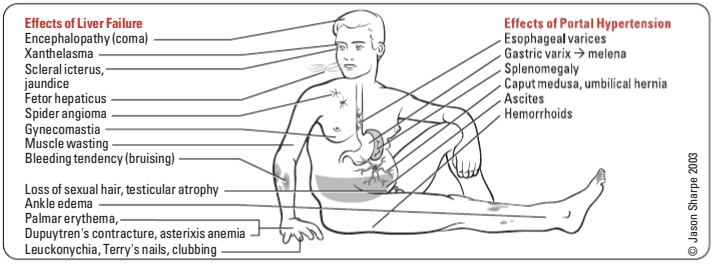


Figure 14. Clinical features of liver disease

Hepatocellular Carcinoma

- see General Surgery and Thoracic Surgery, GS53

Liver Transplantation

- see General Surgery and Thoracic Surgery, GS54

Portal Hypertension

Definition

- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

Pathophysiology

- 3 sites of increased resistance (remember pressure = flow x resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

Complications

- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

Portal Hypertension

Signs
- Esophageal varices
- Melena
- Splenomegaly
- Ascites
- Hemorrhoids

Management
- β-blockers
- Nitrates
- Shunts (e.g. TIPS)

Treatment
- non-selective β-blockers (propranolol, nadolol, carvedilol) decrease risk of bleeding from varices; PREDESCI trial (Lancet 2019;393:1597-1608) showed that non-selective β-blockers in cirrhotic patients with portal hypertension lowers risk of decompensation (particularly ascites)
- TIPS: to decrease portal venous pressure
  - radiologically inserted stent between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute variceal bleeding or prevent rebleeding or treat ascites
  - complications: hepatic encephalopathy, right sided heart failure, deterioration of hepatic function
  - contraindicated with severe liver dysfunction, uncontrolled hepatic encephalopathy, and congestive heart failure

Hepatic Encephalopathy

Definition
- spectrum of potentially reversible neuropsychiatric syndromes secondary to hepatic insufficiency and/or portosystemic shunting, diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

Pathophysiology
- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain

Precipitating Factors
- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (SBP)
- deterioration in hepatic function or superimposed liver disease
- spontaneous portosystemic shunts (e.g. splenorenal shunts) or intentional portosystemic shunts (e.g. TIPS)

Stages
A. minimal hepatic encephalopathy (diagnosed with specialized cognitive testing)
B. overt hepatic encephalopathy (stages I to IV)
- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar response (positive Babinski sign)
- IV: coma (response to painful stimuli only)

Investigations
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out:
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. EtOH withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves
- serum ammonia levels increased, but not often necessary to measure in routine clinical use

Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - routine protein restriction is no longer recommended given patients generally have concurrent malnutrition and muscle wasting; however, vegetable protein (as opposed to animal protein) may help reduce risk of encephalopathy
  - lactulose or lactitol: titrated to achieve 2-3 soft stools/d
    - prevents diffusion of NH_3 (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH_4^+(ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
- oral rifaximin for both acute treatment and maintenance therapy has high level evidence for efficacy
- best acute treatment in patients who cannot take medication orally is lactulose or lactitol enemas

Precipitating Factors for Hepatic Encephalopathy

HEPATICS
Hemorrhage in GI tract/Hypokalemia
Excess dietary protein
Paracentesis
Alkalosis/Anemia
Trauma
Infection
Colon surgery
Sedatives

A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin plus Lactulose with Lactulose Alone in Treatment of Overt Hepatic Encephalopathy
American J Gastroenterol 2013;108:1458-1463
Study: Prospective double-blinded RCT.
Purpose: Efficacy and safety of rifaximin plus lactulose vs. lactulose alone for treatment of overt HE.
Results: Of the patients, 48 (76%) in group A (lactulose plus rifaximin 1200 mg/d, n=63) compared with 29 (50.8%) in group B (lactulose plus placebo, n=57) had complete reversal of HE (P<0.004). There was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose plus placebo (23.8% vs. 49.1%, P<0.05). There were significantly more deaths in group B because of sepsis (group A vs. group B: 7:17, P=0.01), whereas there were no differences because of GI bleed (group A vs. group B: 4:4, P=nonsignificant (NS)) and HRS (group A vs. group B: 4:7, P=NS). Patients in the lactulose plus rifaximin group had shorter hospital stay (5.8±3.4 vs. 8.2±4.6 d, P=0.001).
Conclusion: Combination of lactulose plus rifaximin is more effective than lactulose alone in the treatment of overt HE.

Ascites

Definition
- accumulation of excess fluid in the peritoneal cavity

Etiology

Table 23. Serum-Ascites Albumin Gradient in the Evaluation of Ascites

Serum [Alb] – Ascitic [Alb] >11 g/L (1.1 g/dL) Portal Hypertension Related	Serum [Alb] – Ascitic [Alb] <11 g/L (1.1 g/dL) Non-Portal Hypertension Related
Cirrhosis/severe hepatitis	Peritoneal carcinomatosis
Chronic hepatic congestion (right heart failure, Budd-Chiari)	Peritoneal TB
Massive liver metastases	Pancreatic disease
Portal vein thrombosis	Serositis
Idiopathic portal fibrosis	Nephrotic syndrome*

* In nephrotic syndrome: decreased serum [Alb] to begin with, therefore gradient not helpful

Pathophysiology
- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis
  - overfill hypothesis
  - peripheral arterial vasodilation theory (most popular): as portal hypertension develops in cirrhosis, production of local mediators such as nitric oxide leads to splanchnic arterial vasodilation, ultimately pulling blood away from the systemic circulation and resulting in reduced effective arterial volume, which causes compensatory sodium and fluid retention by the kidneys (i.e. circulatory volume is increased, as per the overfill hypothesis, but effective volume is decreased as per the underfill hypothesis)

Underfill Hypothesis
First step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney

Overfill Hypothesis
Cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily

Diagnosis
- abdominal U/S
- physical exam (clinically detectable when >500 mL)
  - bulging flanks, flank dullness, shifting dullness, fluid-wave test positive
  - most sensitive symptom: ankle swelling

Investigations
- diagnostic paracentesis
  - 1st aliquot: cell count and differential
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis; TG and chylomicrons if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

Serum Ascites Albumin Gradient (SAAG) = serum albumin – ascites albumin
>11 g/L portal HTN
Ascitic fluid total protein >25 g/L, suggests cardiac portal hypertension
Ascitic fluid total protein <25 g/L, suggests cirrhosis portal hypertension
<11 g/L unrelated to portal HTN

Treatment
- diuretic-sensitive ascites
  - Na^+ restriction (daily sodium intake <2 g)
  - no need for fluid restriction unless significant hyponatremia (e.g. Na^+<120-125 mmol/L)
  - diuretics: spironolactone, furosemide
  - aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - if target weight loss is not achieved and there are no complications, increase dose to achieve target while monitoring for complications
- refractory ascites (diuretics are inadequate or not tolerated)
  - therapeutic paracentesis with IV albumin
  - TIPS in an appropriate patient (no contraindications) with potential transplant-free survival advantage
  - liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis is associated with a high 2 yr mortality

Complication: Primary/Spontaneous Bacterial Peritonitis
- primary/SBP
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: *E. coli* (most common), *Streptococcus, Klebsiella*

- diagnosis
  - absolute neutrophil count in peritoneal fluid >0.25x10^9 cells/L (250 cells/mm ^{3})
  - Gram stain positive in only 10-50% of patients
  - culture positive in <80% of patients (not needed for diagnosis)
- prophylaxis: consider in patients with:
  - cirrhotic with GI bleed: ceftriaxone IV daily or norfloxacin BID x 7 d
  - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
- treatment
  - IV ABx (cefotaxime 2 g IV q8h or ceftriaxone 2 g IV daily is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
  - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

Biliary Tract

Jaundice

• see *Table 2, G6* and *Figures 15 and 16*

Definition
• yellowing of the skin, sclera, and/or mucous membranes due to abnormal deposition of pigmented bilirubin

Signs and Symptoms
• dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
• pruritus: suggests chronic disease, cholestasis
• abdominal pain: suggests biliary tract obstruction from stone or pancreatic/biliary tumour (obstructive jaundice)
• painless jaundice in the elderly: think of pancreatic cancer
• kernicterus: rarely seen in adults due to maturation of blood brain barrier

Investigations
• blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), ± amylase/lipase
• U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
• more detailed evaluation of bile duct ± surrounding structures like pancreas:
  - MRCP: non-invasive
  - EUS: sensitive for stones and pancreatic tumours
  - ERCP: invasive, most accurate, allows for therapeutic intervention
  - PTC: if ERCP fails (endoscopic access not possible)

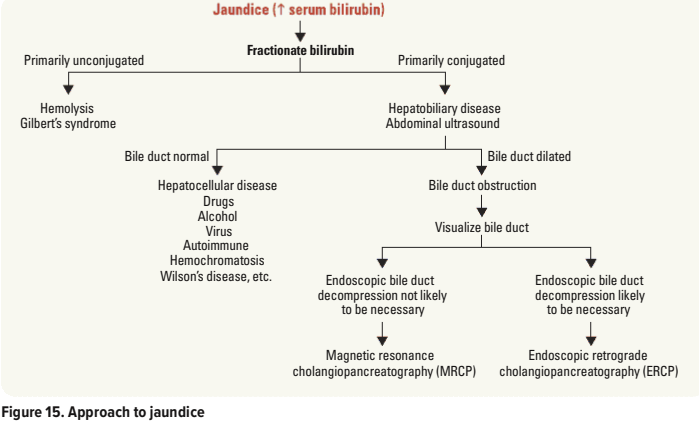


Figure 15. Approach to jaundice

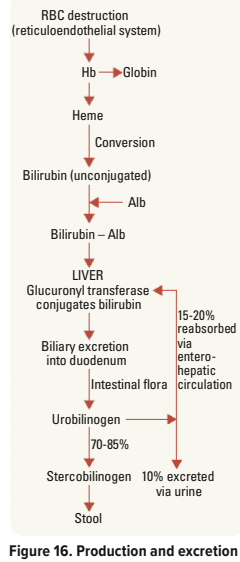


Figure 16. Production and excretion of bilirubin

Gilbert's Syndrome

Definition
- hereditary hyperbilirubinemia due to a deficiency of glucuronyl transferase characterized by repeat episodes of mild asymptomatic jaundice

Etiology/Epidemiology
- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

Clinical Features
- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting, or at times of acute illness; no other clinical implications

Treatment
- reassurance (entirely benign)

Gilbert's Syndrome vs. Crigler-Najjar Syndrome
Gilbert's Syndrome: mild decrease in glucuronyltransferase activity
Crigler-Najjar Syndrome: complete deficiency of glucuronyltransferase

Primary Sclerosing Cholangitis

Definition
- inflammation, fibrosis, and stricturing of biliary tree (intra- and/or extrahepatic bile ducts) from scarring

Etiology
- primary/idiopathic (most common)
  - associated with IBD, more commonly UC, in up to 70-80% of patients (usually male) with PSC
- secondary sclerosing cholangitis (less common)
  - long-term choledocholithiasis
  - cholangiocarcinoma
  - surgical/traumatic injury (iatrogenic)
  - contiguous inflammatory process
  - post-ERCP
  - associated with HIV/AIDS ("HIV cholangiopathy")
  - IgG4-related disease
  - critical illness

Signs and Symptoms
- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction
- may present with jaundice, hepatomegaly, splenomegaly, excoriations secondary to pruritus

Investigations
- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- MRCP and ERCP shows narrowing and dilatations of bile ducts that may result in "beading," both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC
- consider livery biopsy if suspecting small duct variant (accounts for approximately 10% of cases of PSC)

Complications
- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat
- increased incidence of colon cancer in those with concurrent IBD

Treatment
- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma (controversial)
- endoscopic sphincterotomy, biliary stent in selected cases of dominant common bile duct stricture
- ABx for cholangitis
- suppurative cholangitis requires emergency drainage of pus in common bile duct
- liver transplantation appears to be the best treatment for advanced sclerosing cholangitis (>90% 1 yr survival; mean follow-up time from diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that it increases mortality if taken in high doses

Prognosis
- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 yr

Primary Biliary Cholangitis (formerly Primary Biliary Cirrhosis)

Definition
- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

Etiology/Epidemiology
- likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia), RA, thyroiditis)
- affects mainly middle-aged women (M:F=1:9)

Signs and Symptoms
- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal HTN, ascites
- high incidence of osteoporosis

Investigations
- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- elevated IgM
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  - may have: xanthelasmas, xanthomas
- liver biopsy confirms diagnosis and stages severity but is usually not required - elevated ALP for >6 mo and positive AMA are diagnostic
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- "overlap" syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis are possible

Treatment
- drugs that treat the underlying disease:
  - ursodeoxycholic acid (UDCA ; first line treatment)
  - obeticholic acid (if inadequate response to ursodiol)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- repeated monitoring of liver enzymes and LFTs (q 3-6 mo), TSH (annually), and BMD (q 2-4 yr)
- ensure vaccines are updated (notably HAV & HBV); avoid EtOH, smoking
- liver transplant if disease severe, progressive

Prognosis
- can be fatal, although not all asymptomatic patients show progression
- treatment improves prognosis - response to treatment with UDCA (normalization or near-normalization of ALP) is associated with survival comparable to age- and sex-matched controls

Table 24. Primary Sclerosing Cholangitis vs. Primary Biliary Cholangitis

	Primary Sclerosing Cholangitis	Primary Biliary Cholangitis
Predominant Gender	Male	Female
Associated Comorbidities	IBD, especially UC	Other autoimmune disorders (Sjögren's, CREST, RA)
Affected Ducts	Both intra- and extrahepatic	Intrahepatic only
Investigations	ERCP/MRCP (narrowing and dilatations of ducts visualized)	Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)

MRCP/ERCP
Absence of narrowing in PBC
Narrowing of intra- and extrahepatic ducts in PSC

Endoscopic or Surgical Step-Up Approach for Infected Necrotising Pancreatitis: A Multicentre Randomised Trial
Lancet 2018;391:51-58
Purpose: To compare the outcomes of endoscopic vs. the standard surgical removal of infected necrotising pancreatitis.
Study: RCT.
Population: 98 patients with pancreatic or extrapancreatic necrosis were randomized to either endoscopic removal or surgical removal of the infected necrosis.
Outcomes: Major complications and death at 6 mo follow-up.
Results: The primary endpoints of mortality and major complications were the same in the two groups, but the endoscopic group had shortened hospital stays and less pancreatic fistulae.
Conclusions: Three points are worth emphasizing: (1) necrotising pancreatitis is a severe disease: about 15% in each group died; (2) it is best to wait at least 4 wk after the necrosis has developed to allow it to be encapsulated; (3) the management of severe acute pancreatitis should include experts skilled in therapeutic endoscopy.

Biliary Colic, Cholecystitis

- see General Surgery and Thoracic Surgery, GS56

Ascending Cholangitis

- see General Surgery and Thoracic Surgery, *Acute Cholangitis*, GS58

Definition
- infection of the biliary tree

Etiology
- stasis in the biliary tract due to obstruction or stricture
- bacteria
  - *E. coli, Klebsiella, Enterobacter, Enterococcus*
  - coinfection with *Bacteroides* and *Clostridia* can occur

Charcot's Triad
RUQ pain
Fever
Jaundice

Reynolds' Pentad
Charcot's triad
Hypotension
Altered mental status

Signs and Symptoms
- Charcot's triad: fever, RUQ pain, jaundice (50-70%)
- Reynolds' pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

Investigations
- evidence of systemic inflammation (increased WBC, increased CRP)
- usually increased ALP and bilirubin, ALT variably elevated (can be markedly increased if acute obstruction from common bile duct (CBD) stone)
- blood culture
- abdominal U/S: CBD dilation, stricture, stones

Treatment
- most important is drainage, ideally via ERCP; perform by percutaneous biliary or by surgical routes (least often) if ERCP not possible
- antibiotic therapy: broad spectrum to cover Gram-negatives, Enterococcus, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

Prognosis
- good with effective drainage and ABx in mild to moderate cases
- high mortality (~50%) in patients with Reynolds' pentad

Pancreas

Pancreatic Enzyme Abnormalities

Causes of Increased Serum Amylase
- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

Causes of Increased Serum Lipase
- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure

Pancreatic Enzymes

TALC
Trypsin
Amylase
Lipase
Chymotrypsin

When serum amylase >5x normal, the cause is almost always pancreatitis or renal disease

Acute Pancreatitis

Etiology (most common are alcohol and gallstones)
- **I**diopathic: thought to be hypertensive sphincter or microlithiasis
- **G**allstones (45%)
- **E**thanol (35%)
- **T**umours: pancreas, ampulla, choledochocele
- **S**corpion stings
- **M**icrobiological
  - bacterial: *Mycoplasma, Campylobacter*, TB, *M. avium intracellulare, Legionella, Leptospira*
  - viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
  - parasites: ascariasis, clonorchiasis, echinococcosis
- **A**utoimmune: IgG4-related disease, SLE, *polyarteritis nodosa* (PAN), CD
- **S**urgery/trauma
  - manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer
- **H**yperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), hypercalcemia, hypothermia
- **E**mboli or ischemia
- **D**rugs/toxins
  - azathioprine, mercaptopurine, furosemide, estrogens, methyldopa, H_2-blockers, valproic acid, ABx, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

When thinking about the causes of acute pancreatitis remember: **I GET SMASHED,** but vast majority due to gallstones or ethanol

Pathophysiology
- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
- in ethanol-related pancreatitis, pathogenesis is unknown
- in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in *SPINK1* gene, which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

Pathology
- mild (interstitial)
  - peri-pancreatic fat necrosis
  - interstitial edema
- severe (necrotic)
  - extensive peri-pancreatic and intra-pancreatic fat necrosis
  - parenchymal necrosis and hemorrhage → infection in 60%
  - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- severity of clinical features may not always correlate with pathology
- 3 phases
  - local inflammation + necrosis → hypovolemia
  - systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  - local complications >2 wk after presentation → fluid collection (pseudocyst) or tissue collection (necrosis), sterile or infected

Cullen's Sign
Sensitive, not specific for acute pancreatitis

Grey-Turner's Sign
Flank ecchymosis

Signs and Symptoms
- pain: epigastric, noncolicky, constant
- can radiate to back
- may improve when leaning forward (Inglefinger's sign)
- tender rigid abdomen; guarding
- N/V
- abdominal distention from paralytic ileus
- fever: chemical, not due to infection
- jaundice: compression or obstruction of bile duct
- Cullen's/Grey-Turner's signs
- tetany: transient hypocalcemia
- hypovolemic shock: can lead to renal failure
- acute respiratory distress syndrome
- coma

Increased Amylase
- Sensitive, not specific for acute pancreatitis

Increased Lipase
Higher sensitivity and specificity
Stays elevated longer

Investigations
- increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >150 specific for biliary cause
- increased WBC, glucose, low calcium
- imaging: CT most useful for diagnosis and prognosis
  - x-ray: "sentinel loop" (dilated proximal jejunum), calcification, and "colon cut-off sign" (colonic spasm)
  - U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  - CT scan with IV contrast: most useful when done >1 d after presentation, helpful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  - ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

Classification
- interstitial edematous vs. necrotizing
- mild, moderate, severe

Prognosis
- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to:
  - shock
  - pulmonary edema
  - multi-organ dysfunction syndrome
  - GI ulceration due to stress
  - death
    - numerous scales to describe severity: probably most useful is proportion of pancreas not taking up contrast on CT done 48 h after presentation (necrotic pancreas does not take up the contrast dye)
    - presence of organ failure, particularly organ failure that persists >48 h, is associated with worse outcomes

Table 25. Collections in Pancreatitis (Revised 2012 Atlanta Classification)

	Liquid	Solid
Acute	Acute peripancreatic fluid collection (APFC)	Acute necrotic collection (ANC)
Chronic	Pancreatic pseudocyst	Walled-off necrosis (WON)

All of these collections are classified as infected or not infected

Treatment
- goals (only supportive therapy available)
  1. hemodynamic stability
  2. analgesia
  3. oxygen
  4. stop progression of damage (difficult)
  5. treat local and systemic complications
- antibiotic use in infection (cephalosporins, imipenem), not indicated to prevent infection, although without aspiration/biopsy can be difficult to distinguish infection from non-infected inflammation
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
  - beware third spacing of fluid, monitor urine output carefully
- NG suction (lets pancreas rest) if vomiting, stomach very dilated
- endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
- nutritional support: NJ feeding tube or TPN if cannot tolerate enteric feeds
  - recent evidence supports NG enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, aprotinin, H_2-blockers, peritoneal lavage
- follow clinically and CT or U/S to exclude complications
- chief role of invasive intervention is to drain fluid collection, excise necrotic tissue (necrosectomy), especially indicated if pseudocyst or walled-off necrosis is infected
  - try to delay for >2 wk to allow demarcation between viable and necrotic tissue, better done endoscopically or radiologically, rather than surgically if technically possible

Late Complications
- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  - drain preferably: endoscopic, percutaneous under radiological guidance, surgical if less invasive methods fail
- infected necrosis/abscesses: ABx + percutaneous drainage, endoscopic preferable to surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: DM, pancreatic duct damage

Gallstones only cause acute pancreatitis (not chronic pancreatitis)

Symptoms of Chronic Pancreatitis
- Abdominal pain
- Diabetes
- Steatorrhea

Etiology = Almost Always Alcohol

Treatment
- EtOH abstinence
- Pancreatic enzyme replacement
- Analgesics
- Pancreatic resection if ductular blockage

Chronic Pancreatitis

Definition
- irreversible damage to pancreas characterized by
  1. pancreatic cell loss (from necrosis)
  2. inflammation
  3. fibrosis

Etiology/Pathophysiology
- **T**oxic-metabolic
  - EtOH (most common)
    - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
    - changes composition of pancreatic juice (e.g. increase viscosity)
    - decreases pancreatic secretion of pancreatic stone protein (lithostathine), which normally solubilizes calcium salts
      - precipitation of calcium within pancreatic duct results in duct and gland destruction
    - toxic effect on acinar and duct cells - directly or via increasing free radicals
    - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
    - varying degrees of ductular dilatation, strictures, protein plugs, calcification
    - no satisfactory theory to explain why only a minority of individuals with EtOH use disorder develop pancreatitis
  - smoking
  - hypercalcemia
  - hypertriglyceridemia
  - medications
- **I**diopathic
- **G**enetic
- **A**utoimmune pancreatitis/steroid-responsive pancreatitis (e.g. IgG4-related disease)
- **R**ecurrent acute pancreatitis/severe acute pancreatitis
- **O**bstructive (e.g. pancreas divisum, ampullary stenosis)

Signs and Symptoms
- early stages
  - recurrent attacks of severe abdominal pain (upper abdomen and back)
  - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
  - steatorrhea (maldigestion) when >90% of function is lost
  - diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed

When to Call the Surgeon in Acute Pancreatitis?
Endoscopic Transgastric vs. Surgical Necrosectomy for Infected Necrotizing Pancreatitis: A Randomized Trial JAMA 2012;307:1053-1061
Once it was recognized that severe acute (necrotizing) pancreatitis had a terrible prognosis because of an exuberant inflammatory response leading to multiorgan failure, pancreatectomy was attempted. However, contrary to the expected favourable results, clinical experience has shown that surgical pancreatectomy is usually not helpful, perhaps because once the inflammatory cascade starts, it persists as a self-perpetuating cycle. The problems caused by acute pancreatitis can be thought of as widespread burn initiated by inflammation in the pancreas, but having little to do with ongoing problems within the pancreas itself. Studies suggest that the only compelling indication for surgery is infected necrotizing pancreatitis not responding to ABx. As predicted, without removal of such infected pancreatic tissue, death is likely from sepsis.
In this recent randomized trial, transgastric necrosectomy, an endoscopic technique that also removes infected necrotic pancreatic tissue, reduced both a composite endpoint of major pancreatitis complications (especially new onset organ failure) and the pro-inflammatory response (as measured by serum IL-6 levels) to a greater extent than surgical necrosectomy. Of course, not all necrotic collections are in areas amenable to endoscopic intervention, and the advice of an experienced surgeon should always be welcomed in severe acute pancreatitis, but the role of surgery in this previously considered surgical disease is rapidly diminishing.

Investigations
- laboratory
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
  - stool elastase is low in steatorrhea
- abdominal x-ray: pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts, most sensitive test
- 72 h fecal fat test: measures exocrine function, fecal elastase preferable
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive

Treatment
- most common problem is pain, difficult to control
- general management
  - complete abstinence from EtOH
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas "burns out"
- endoscopy: sphincterotomy, stent if duct is dilated, remove stones from pancreatic duct
- surgery: drain pancreatic duct (pancreaticojejunostomy) if duct is dilated (more effective than endoscopy); resect pancreas if duct is contracted
- steatorrhea
  - pancreatic enzyme replacement
  - neither endoscopy nor surgery can improve pancreatic function

Autoimmune Pancreatitis

- most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice ± abdominal pain)

Investigations
- histology: lymphocyte and plasma cell infiltration of pancreas
- imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage-shaped, low density rim around pancreas
- serology: increased serum IgG4 in type 1
- other organ involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

Treatment
- responds to prednisone
- for refractory patients, consider immunomodulators (azathioprine, mycophenolate mofetil, methotrexate) or rituximab

Clinical Nutrition

Determination of Nutritional Status

Challenging to Differentiate Markers of Malnutrition from Markers of Disease
- most important feature in assessing the need for nutritional support is weight loss (expressed as change in body mass index (kg/m^2))
- Subjective Global Assessment divides nutritional status into A) adequately nourished, B) mild or moderate malnutrition, and C) severe malnutrition in order to identify those who will benefit from nutritional support
- includes weight change in past 6 mo, weight change in past 2 wk, dietary intake change, current dietary intake, GI symptoms, functional capacity, effect of disease on nutritional requirements and physical examination, including loss of subcutaneous fat/muscles wasting/edema/ascites

Table 26. Small Bowel Nutrient Absorption

	Fe^{3+}	CHO	Proteins, Lipids Na^+, H_2O	Bile Acids	Vitamin B_{12}
Duodenum	+++	+++	+++	+	
Jejunum	+	+	++	+	+
Ileum	+	+	++	+++	+++

Determining Nutritional Requirements
- calories: total energy expenditure (TEE) = resting energy expenditure (REE) x stress factor (e.g. 1.7 for burns) usually works out to be 25-35 kcal/kg depending on how disease affects metabolism, with IV nutrition delivered as about 60% carbohydrate, 40% fat. Current trend is to provide fewer calories ("permissive underfeeding"), especially in ICU, to prevent hyperglycemia
- protein: 1-2 g/kg/d, depending on effect of disease on protein metabolism. In disease, a greater proportion of energy expenditure comes from protein than in health
- electrolytes, minerals, and vitamins also required

Indications for Aggressive Nutritional Support:
- inability to meet nutritional needs; logical, but convincing evidence from literature not available for ICU and other acute illnesses
- evidence that nutritional support improves outcome available for (1) short bowel syndrome (home TPN), (2) before major abdominal or thoracic surgery if there is substantial malnutrition, (3) before therapy for cancer of esophagus, head, and neck, (4) decompensated alcoholic liver disease, (5) pancreatitis (acute and chronic). May be helpful for other indications also, but insufficient data
- nutritional support at best prevents protein loss but usually no gain

Enteral Nutrition

Definition
- EN (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
  - nasogastric (NG), or nasojejunal (NJ) if nutritional support required for brief time; percutaneous endoscopic gastrostomy ("G-tube" or "PEG tube")/percutaneous endoscopic jejunostomy (J-tube) if nutritional support required for more than 1 mo
- tubes can be placed endoscopically, radiologically, or surgically

Most Common Indications for Artificial Nutrition Support
- Preexisting nutritional deprivation
- Anticipated or actual inadequate energy intake by mouth
- Significant multiorgan system disease

Indications
- oral feeding inadequate or contraindicated

Feeds
- polymeric feeds contain whole protein, carbohydrates, fat as a liquid, and may or may not have fibre added
- elemental feeds contain protein (as amino acids), carbohydrates (as simple sugars), and are low in fat content (are therefore high in osmolarity)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

Relative Contraindications
- non-functioning gut (e.g. intestinal obstruction, enteroenteral or enterocutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding

Whenever possible, EN is ALWAYS preferable over PN

Complications
- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnia, azotemia (from excess protein)

Parenteral Nutrition

Definition
- PN is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications
- short-term (<1 mo)
  - use whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively, and in difficult-to-control sepsis
  - preoperative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)

- some evidence for efficacy, but convincing data not available for:
  - radiation/chemotherapy-induced enteritis
  - AIDS with wasting diarrhea
  - severe acute pancreatitis
- long-term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of small bowel (e.g. small bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection

Relative Contraindications
- functional GI tract available for EN
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem

Enteral vs. Parenteral Nutrition for Acute Pancreatitis Cochrane DB Syst Rev 2010;1:CD002837
Purpose: Compare EN vs. TPN on mortality, morbidity, and hospital stay in patients with pancreatitis.
Study Selection: RCTs of TPN vs. EN in pancreatitis.
Results: Eight trials (n=348) were included. EN decreases RR of death (0.50), multiple organ failure (0.55), infection (0.39), and other local complications (0.70). It also decreased hospital stay by 2.37 d.
Conclusion: EN reduces mortality, organ failure, infections, and length of hospital stay in patients with pancreatitis.

Complications of PN
- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: congestive heart failure, hyperglycemia, gallstones, cholestasis, electrolyte abnormalities, micronutrient deficiency

Enteral Nutrition Preferable to Parenteral Nutrition
- fewer serious complications (especially sepsis)
- nutritional requirements better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids with EN
- nutrients in the intestinal lumen have a trophic effect (prevent atrophy of the gut and pancreas)
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Common Medications

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Proton Pump Inhibitors (H^+K^+-ATPase inhibitors)	omeprazole	Losec®/ Prilosec®	20 mg PO once daily	Inhibits gastric enzymes H^+/K^+-ATPase (proton pump)	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of *H. pylori* (combined with ABx)	Hypersensitivity to drug	Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)
	lansoprazole or dexlansoprazole	Prevacid® Dexilant®	Oral therapy: lansoprazole 15-30 mg once daily (before breakfast), dexlansoprazole 30-60 mg once daily (does not need to be taken before breakfast)	Same as above	Same as above	Same as above	Same as above
	pantoprazole	Pantoloc® Protonix®	40 mg PO once daily for UGIB: 80 mg IV bolus then 8 mg/h infusion	Same as above	Same as above and UGIB	Same as above	Same as above
	rabeprazole	Pariet®/ Aciphex®	40 mg PO once daily	Same as above	Same as above	Same as above	Same as above
	esomeprazole	Nexium®	20-40 mg PO once daily	Same as above	Same as above	Same as above	Same as above
Histamine H_2 Receptor Antagonists	ranitidine* *ranitidine drugs recalled in 2019 due to impurity concerns	Zantac®*	300 mg PO once daily or 150 mg BID IV therapy: 50 mg q8 h (but tachyphylaxis a problem)	Inhibits gastric histamine H_2 receptors	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD; not useful for acute GI bleeds	Hypersensitivity to drug	Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression
	famotidine	Pepcid®	Oral therapy: duodenal/ gastric ulcers: 40 mg qhs GERD: 20 mg BID IV therapy: 20 mg BID	Same as above	Same as above	Same as above	Same as above
Stool Softener	docusate sodium	Colace®	100-400 mg PO once daily, divided in 1-4 doses	Promotes incorporation of water into stool	Relief of constipation	Presence of abdominal pain, fever, N/V	Throat irritation, abdominal cramps, rashes

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Osmotic Laxatives	lactulose	Lactulose Constulose®	Constipation: 15-30 mL PO once daily to BID Encephalopathy: 15-30 mL BID to QID	Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid in the colon, increases osmotic colonic contents, increases stool volume	Chronic constipation, prevention, and treatment of portal-systemic encephalopathy	Patients who require a low galactose diet	Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage
	PEG3350	Lax-a-day® RestoraLAX® Golytely®	Constipation: 17 g powder dissolved in 4-8 oz liquid PO once daily	Osmotic agent causes water retention in stool and promotes frequency of stool	Relief of constipation Colonoscopy prep	Hypersensitivity to drug	Abdominal distension, pain, anal pain, thirst, nausea, rigor, tonic-clonic seizures (rare)
	magnesium hydroxide	Milk of Magnesia/ Pedia-Lax®	Constipation (adult): 400 mg/5 mL: 30-60 mL PO qhs	Osmotic retention of fluid which distends the colon and increases peristaltic activity	Relief of constipation	Patients with myasthenia gravis or other neuromuscular disease	Renal impairment Abdominal pain, vomiting, diarrhea
Stimulant Laxatives	senna	Senokot®	Tablets: 1-4 PO qhs Syrup: 10-15 mL PO qhs	Induce peristalsis in lower colon	Constipation	Patients with acute abdomen	Abdominal cramps, discolouration of breast milk, urine, feces, melanosis coli and atonic colon from prolonged use (controversial)
	bisacodyl	Bisacodyl®	5-30 mg PO once daily (start at 10 mg for bowel preparation)	Enteric nerve stimulation and local contact-induced secretory effects Colonic movements	Constipation Preparation of bowel for procedure	GI obstruction Gastroenteritis	Abdominal colic, abdominal discomfort, proctitis (with suppository use), diarrhea
Bulk Laxatives	psyllium	Metamucil®	Start at one heaping tablespoon daily	Increases stool bulk → water retention in stool	Constipation	Hypersensitivity to drug GI obstruction	GI obstruction, diarrhea, constipation, abdominal cramps
Guanylate Cyclase C Agonist	linaclotide	Constella®	75-145 µg once daily	Opens water channels in bowel epithelial cells to add water to stool	Chronic constipation IBS-constipation	Children	Diarrhea
Antidiarrheal Agents	loperamide	Imodium®	Acute diarrhea: 4 mg PO initially, followed by 2 mg after each unformed stool	Acts as antidiarrheal via cholinergic, noncholingeric, opiate, and non-opiate receptor-medicated mechanisms; decreases activity of myenteric plexus	Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies, and other intestinal resections	Children <2 yr, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute UC or pseudomembranous colitis associated with broad-spectrum ABx	Abdominal pain or discomfort, drowsiness or dizziness, tiredness, dry mouth, N/V, hypersensitivity reaction
	diphenoxylate/ atropine	Lomotil®	5 mg PO TID to QID	Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time	Adjunctive therapy for diarrhea, as above	Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhea caused by enterotoxin producing bacteria	Dizziness, drowsiness, insomnia, headache, N/V, cramps, allergic reaction
	eluxadoline	Viberzil®	75-100 mg BID	Bowel opioid modulator	IBS Diarrhea	Pancreatic disease, excess EtOH, gallstones or other biliary disease	Pancreaticobiliary pain including sphincter of Oddi dysfunction
Antiemetics	dimenhydrinate	Gravol®	25-50 mg PO/IV/IM q4-6 h PRN	Competitive H_1 receptor antagonist in GI tract, blood vessels, and respiratory tract. Blocks chemoreceptor trigger zone. Diminishes vestibular simulation and disrupts labyrinthine function through central anticholinergic action	Motion sickness, radiation sickness, postoperative vomiting, and drug-induced N/V	Hypersensitivity to drug	Xerostomia, sedation
	prochlorperazine	Stemetil®	5-10 mg PO/IV/IM BID-TID PRN	D_1, D_2receptor antagonist in chemoreceptor trigger zone and α-adrenergic and anticholinergic effects Depresses reticular activating system (RAS) affecting emesis	Postoperative N/V, antipsychotic, anxiety	Hypersensitivity to drug	Dystonia, extrapyramidal symptoms (EPS), seizure, NMS (rarely)
	metoclopramide	Maxeran®	10 mg IV/IM q2-3 h pm, 10-15 mg PO QID (30 min before meals and qhs)	Dopamine and 5-HT receptor antagonist in chemoreceptor trigger zone. Enhances response to ACh in upper GI tract, enhancing motility and gastric emptying. Increases LES tone	GERD, diabetic gastroparesis, postoperative and chemotherapy induced N/V, migraines, constipation	Hypersensitivity to drug, GI obstruction, perforation, hemorrhage, pheochromocytoma, seizures, and EPS	Restlessness, drowsiness, dizziness, fatigue, EPS, some rare serious side effects include NMS, agranulocytosis

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
	ondansetron	Zofran®	Depends on procedure, generally 8-16 mg PO	Selective 5-HT_3 receptor antagonist in central chemoreceptor trigger zone and peripherally on vagus nerve	N/V caused by cancer chemotherapy and radiation therapy; multiple off label uses, including gastroenteritis N/V	Morphine, hypersensitivity to drug	Constipation, diarrhea, increased liver enzymes, headache, fatigue, malaise, cardiac dysrhythmia
	granisetron	Kytril®	1 mg PO BID (for nausea from chemotherapy/ radiation)	Same as above	N/V caused by cancer chemotherapy and radiation therapy	Same as above	Constipation, prolonged QT interval (rarely)
Prokinetic Agents	domperidone	Motilium®	GI motility disorder (e.g. gastroparesis): 10 mg TID	peripherally acting D_2 receptor blocker, main effect in the upper GI tract (i.e. increased esophageal peristalsis, gastric motility), antiemetic properties	upper GI motility disorders (e.g. gastroparesis, subacute gastritis), prevention of nausea associated with dopamine-agonists	hypersensitivity to domperidone, prolonged QT interval, prolactinoma, electrolyte disturbances, CYP3A4 inhibitors, mechanical GI obstruction or perforation, GI hemorrhage, severe hepatic dysfunction, children <2 yr	cardiac arrhythmia (use lowest dose for shortest duration) and hyperprolactinemia causing hypogonadism, breast engorgement, and galactorrhea
	prucalopride	Resotran® Motegrity®	2 mg PO QD	high affinity 5-HT_4 agonist, main effect in the lower GI tract (i.e. increased colonic peristalsis, ameliorates gastroparesis)	chronic idiopathic constipation	hypersensitivity to prucalopride, GI obstruction or perforation, severe inflammation co-morbidity (e.g. Crohn's disease, UC, toxic megacolon)	headache, fatigue, dizziness, abdominal pain, N/V, diarrhea, abdominal distention
Aminosalicylates (5-ASAs)	mesalamine	Pentasa® Salofalk® Asacol® Mesasal®	CD: 1 g PO TID/QID Active UC: 1 g PO QID Maintenance UC: 1.6 g PO divided doses daily also as suppositories and enemas	5-ASA: Blocks arachidonic acid metabolism to prostaglandins and leukotrienes	Mild to moderate UC	Hypersensitivity to mesalamine salicylates; Asacol® contains phthalate, potential urogenital teratogenicity for male fetus	Abdominal pain, constipation, arthralgia, headache
	sulfasalazine	Salazopyrin®	3-4 g/d PO in divided doses	Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component	Mild to moderate UC	Hypersensitivity to sulfasalazine, sulfa drugs, salicylates; intestinal or urinary obstruction, porphyria	Rash, loss of appetite, N/V, headache, oligospermia (reversible)
Immuno-suppressive Agents	6-mercaptopurine (6-MP)	Purinethol®	CD: 1.5 mg/kg/d PO	Immunosuppressive	IBD: active inflammation and to maintain remission	Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hypersensitivity to azathioprine, pregnancy	Pancreatitis, bone marrow suppression, increased risk of cancer
	azathioprine	Azasan® Imuran®	IBD: 2-3 mg/kg/d PO	Same as above	Same as above	Same as above	Same as above
	prednisone		Induction of remission for acute exacerbations: 20-40 mg PO once daily; taper 2.5-5 mg/wk until discontinued	Anti-inflammatory	Symptomatic moderate to severe CD and UC	Hypersensitivity to prednisone, systemic fungal infections	Hyperglycemia, insomnia, osteoporosis, weight gain, increased risk of infections
Biologics	infliximab	Remicade®	5-10 mg/kg IV over 2 h	Monoclonal antibody to TNFα	Medically refractory CD	Heart failure, moderate to severe, doses >5 mg/kg	Reported cases of reactivated TB, PCP, lymphoma, other infections Other TNFα share similar serious side effects
	adalimumab	Humira®	CD induction: four 40 mg SC on day 1, then 80 mg 2 wk later (day 15) CD maintenance: 40 mg every other wk beginning day 29	Monoclonal antibody to TNFα	Medically refractory CD or poor response to infliximab	Hypersensitivity to adalimumab Severe infection Moderate-to-severe heart failure	Headaches, skin rashes, upper respiratory tract infection
	golimumab	Simponi®	RA: 2 mg/kg at wk 0, 4, and then every 8 wk thereafter (use with methotrexate) UC induction: 200 mg SC at wk 0, then 100 mg at wk 2 UC maintenance: 50 mg every 4 wk	Monoclonal antibody to TNFα	Active ankylosing spondylitis Psoriatic arthritis Moderate-to-severe active RA (combined with methotrexate) UC: medically refractory UC	Hypersensitivity to golimumab or latex Severe infection Moderate-to-severe heart failure	
	vedolizumab	Entyvio®	CD/UC: 300 mg at 0, 2, 6 wk and then every 8 wk thereafter	Monoclonal antibody to α4β7 integrin	Medically refractory CD/UC, including other TNFα inhibitors and corticosteroids	Hypersensitivity to vedolizumab	Infections, liver injury, and progressive multifocal leukoencephalopathy
	ustekinumab	Stelara®	Induction: single IV weight-based dose on day 1 Maintenance: 90 mg subcutaneous injection every 8 wk	Monoclonal antibody to IgG1K, inhibits signals by IL-12 and IL-23	Moderate to severe CD and UC	Hypersensitivity to ustekinumab	Infections, headaches, joint pain, fever, N/V

Table 27. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Small Molecules	tofacitinib	Xeljanz®	5-10 mg BID	JAK inhibitor	UC	TB, hepatitis B	Infections, macro-cardiac events, thrombosis (e.g. PE, DVT)
Antibiotics	rifaximin	Zaxine®	550 mg BID or TID	Non-absorbable antibiotic, affects dysbiosis of microbiome	Hepatic encephalopathy Non-constipation IBS Traveller's diarrhea	Nil	Nil

Landmark Gastroenterology Trials

Trial Name	Reference	Clinical Trial Details
PEPTIC ULCER DISEASE		
FAMOUS	Lancet 2009;374:119-25	**Title:** Famotidine for the Prevention of Peptic Ulcers and Oesophagitis in Patients Taking Low-dose Aspirin (FAMOUS): A Phase III, Randomised, Double-blind, Placebo-controlled Trial **Purpose:** Evaluate the efficacy of famotidine in the prevention of peptic ulcers and erosive esophagitis, in patients receiving low-dose aspirin. **Methods:** Patients without erosions or ulcers on upper endoscopy, currently on low-dose aspirin, were randomized to famotidine 20 mg BID or placebo. The primary endpoint was development of new stomach ulcers. **Results:** At 12 wk, gastric ulcers occurred in 3.4% of famotidine patients and 15% of placebo-matched patients (OR 0.20; 95% CI 0.09 to 0.47; P=0.0002). Duodenal ulcers developed in 0.5% of famotidine patients and 8.5% of placebo patients (OR 0.05; 95% CI 0.01 to 0.40; P=0.0045). **Conclusions:** Famotidine is effective in the prevention of gastric and duodenal ulcers, and erosive esophagitis in patients taking low-dose aspirin.
INFLAMMATORY BOWEL DISEASE		
SONIC	NEJM 2010;362:1383-95	**Title:** Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease **Purpose:** Compare the efficacy and safety of infliximab and azathioprine therapy alone or in combination, in patients with CD. **Methods:** CD patients who had not undergone previous biologic or immunosuppressive therapy were randomized to infliximab 5 mg/kg IV infusion or 2.5 mg oral azathioprine, or combination therapy of both drugs. **Results:** Among patients receiving combination therapy, 56.8% were in steroid-free remission, compared with 44.4% of patients receiving infliximab monotherapy, and 30% receiving azathioprine monotherapy (P<0.001 for comparison with combination; P=0.06 for comparison with infliximab). **Conclusions:** Patients' CD treated with infliximab monotherapy or infliximab-azathioprine combination had better corticosteroid-free remission than azathioprine monotherapy recipients.
A Comparison of Methotrexate with Placebo for the Maintenance of Remission in Crohn's Disease	NEJM 2000;342:1627-32	**Title:** A Comparison of Methotrexate with Placebo for the Maintenance of Remission in Crohn's Disease **Purpose:** Evaluate the role of methotrexate in maintaining remission of CD. **Methods:** Patients with chronically active CD who entered remission were randomized to methotrexate 15 mg IM or placebo for 15 wk. The primary endpoint was rates of remission at wk 40. **Results:** At the follow-up period of 40 wk, 65% of methotrexate patients were in remission compared to 39% of patients in the placebo group (risk reduction 26.1%; 95% CI 4% to 47.8%; P=0.04). None of the methotrexate patients reported serious adverse events. **Conclusions:** Patients with CD in remission saw increased remission rates and fewer relapse treatments at 40 wk.
Adalimumab Induction Therapy for Crohn's Disease Previously Treated with Infliximab	Ann Intern Med 2007;146:829-38	**Title:** Adalimumab Induction Therapy for Crohn's Disease Previously Treated with Infliximab **Purpose:** Determine the efficacy of adalimumab in symptomatic CD patients despite infliximab treatment. **Methods:** 325 adults with moderate-severe active CD were randomized to induction doses of adalimumab 160 mg and 80 mg at 0 and 2 wk respectively, or time-matched placebo. The primary endpoint was induction of remission at 4 wk. **Results:** Remission was achieved at 4 wk in 21% of adalimumab patients compared with 7% of placebo patients (95% CI 6.7% to 21.6%). **Conclusions:** Adalimumab induces remission more frequently than placebo in adult patients with symptomatic CD despite infliximab therapy.
UNIFI	NEJM 2019;381:1201-14	**Title:** Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis **Purpose:** Determine the effectiveness of ustekinumab as induction and maintenance therapy in patients with UC. **Methods:** 961 patients with moderate-severe UC were randomized to IV induction ustekinumab (130 mg), or placebo. The primary endpoint was clinical remission determined by the Mayo scale. **Results:** The primary endpoint occurred in 15.6% of patients in the intervention group compared with 5.3% of placebo patients (P<0.001). The incidence of serious adverse events was similar between groups. **Conclusions:** Ustekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe UC.
VARSITY	NEJM 2019;381:1215-26	**Title:** Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis **Purpose:** Compare efficacy of vedolizumab versus adalimumab in patients with moderate-severe UC. **Methods:** Adults with moderate-severe active UC were randomized to IV infusions of vedolizumab 300 mg or subcutaneous adalimumab 40 mg (total weekly dose 160 mg). The primary outcome was clinical remission at wk 52 as determined by the Mayo scale. **Results:** At wk 52, clinical remission was observed in 31.3% of vedolizumab patients compared to 22.5% of adalimumab patients (95% CI 2.5 to 15.0; P=0.006). Steroid-free remission occurred in 12.6% of vedolizumab patients and 21.8% of adalimumab patients (95% CI 18.9 to 0.4). **Conclusions:** In patients with moderate-to-severe UC, vedolizumab was superior to adalimumab with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.

Trial Name	Reference	Clinical Trial Details
LIVER DISEASE		
MELD Score as A Predictor Of Death in Chronic Liver Disease	Gastroenterology 2003;124:91-96	**Title:** MELD Score as A Predictor Of Death in Chronic Liver Disease **Purpose:** Assess the capability for the MELD score to correctly rank potential liver transplant recipients. **Methods:** The MELD score was prospectively applied to estimate 3-mo mortality in 3437 adult liver transplant candidates with chronic liver disease. **Results:** Waiting list mortality increased directly in proportion to the MELD score. Using 3-mo mortality as the endpoint, the ROC curve for MELD was 0.83 compared to 0.76 for the Child-Turcotte-Pugh score. **Conclusions:** MELD score can be applied for allocation of donor livers as it accurately predicts 3-mo mortality in patients with chronic liver failure.
PROVE 3	NEJM 2010;362:1292-1303	**Title:** Telaprevir for Previously Treated Chronic HCV Infection **Purpose:** Study the efficacy of telaprevir in patients without a sustained virologic response to peginterferon therapy. **Methods:** Patients with HCV genotype 1 without sustained virologic response to peginterferon therapy were randomized to one of four telaprevir and peginterferon treatment groups. The primary endpoint was sustained virologic response 24 wk after the last dose. **Results:** The rates of sustained virologic response in the three telaprevir groups were significantly higher than the control group rates (14%, P<0.001, P<0.001, P=0.02). Discontinuation of the drugs due to adverse events was more frequent in the telaprevir groups than in the control group (15% vs. 4%). **Conclusions:** In HCV-infected patients in whom initial peginterferon therapy failed, retreatment with telaprevir in combination with peginterferon and ribavirin was more effective than the latter two alone.
SPRINT-2	NEJM 2011;364:1195-1206	**Title:** Boceprevir for Untreated Chronic HCV Genotype 1 Infection **Purpose:** Evaluate virologic response with additional boceprevir treatment in patients with HCV genotype 1 infection. **Methods:** Previously untreated adults with HCV genotype 1 infection were randomized to placebo plus peginterferon-ribavirin or boceprevir plus peginterferon-ribavirin. The primary endpoint was sustained virologic response. **Results:** A virologic response was achieved in 40% of group 1, 67% in group 2 and 68% in group 3. **Conclusions:** The addition of boceprevir to standard therapy of peginterferon-ribavirin, compared with standard therapy alone, increased rates of sustained virologic response in chronically HCV infected adults.
Rifaximin Treatment in Hepatic Encephalopathy	NEJM 2010;362:1071-81	**Title:** Rifaximin Treatment in Hepatic Encephalopathy **Purpose:** Evaluate the efficacy of rifaximin in the prevention of hepatic encephalopathy secondary to cirrhosis. **Methods:** 299 patients in remission from recurrent hepatic encephalopathy were randomized to rifaximin 550 mg BID or placebo for 6 mo. The primary endpoint was time for the first breakthrough episode. **Results:** Rifaximin reduced the risk of a hepatic encephalopathy episode (hazard ratio 0.42; 95% CI 0.28 to 0.64; P<0.001). A breakthrough episode occurred in 22.1% of rifaximin-treated patients compared to 45.9% of placebo patients (hazard ratio 0.5; 95% CI 0.29 to 0.87; P=0.01). The incidence of adverse events was similar between groups. **Conclusions:** The antibiotic rifaximin was successful in maintaining remission from hepatic encephalopathy and reducing hospitalizations.
Prednisolone or Pentoxifylline For Alcoholic Hepatitis	NEJM 2015;372:1619-28	**Title:** Prednisolone or Pentoxifylline For Alcoholic Hepatitis **Purpose:** To elucidate the benefits of pentoxifylline and prednisolone for the treatments of severe alcoholic hepatitis. **Methods:** Patients with severe alcoholic hepatitis were randomized to one of four groups: double-matched placebo, prednisolone plus matched placebo, pentoxifylline plus matched placebo, or prednisolone plus pentoxifylline. The primary endpoint was mortality at 28 d. **Results:** Mortality at 28 d was 17% in the first group, 14% in the second group, 19% in the third group, and 13% in the fourth group. At 90 d and 1 yr, there were no significant differences between groups. **Conclusions:** For alcoholic hepatitis, prednisolone improved survival at a level below statistical significance. Pentoxifylline did not improve survival.

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GS General and Thoracic Surgery

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Acronyms

5-FU	5-fluorouracil
AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ABI	ankle brachial index
ALND	axillary lymph node dissection
APR	abdominoperineal resection
ARDS	acute respiratory distress syndrome
ATN	acute tubular necrosis
AXR	abdominal x-ray
BRBPR	bright red blood per rectum
BCS	breast conserving surgery
CBD	common bile duct
CEA	carcinoembryonic antigen
CF	cystic fibrosis
CHD	common hepatic duct
CRC	colorectal cancer
CVA	costovertebral angle
CVP	central venous pressure
DCIS	ductal carcinoma in situ
DHEAS	dehydroepiandrosterone sulfate
DIC	disseminated intravascular coagulation
DPL	diagnostic peritoneal lavage
DRE	digital rectal exam
EBL	estimated blood loss
ERCP	endoscopic retrograde cholangiopancreatography
EUA	examination under anesthesia
EUS	endoscopic ultrasound
FAP	familial adenomatous polyposis
FAST	focused abdominal sonography for trauma
FNA	fine needle aspiration
FNH	focal nodular hyperplasia
FOBT	fecal occult blood test
GERD	gastroesophageal reflux disease
GIST	gastrointestinal stromal tumour
GU	genitourinary
HCC	hepatocellular carcinoma
HDGC	hereditary diffuse gastric carcinoma
HIDA	hepatobiliary imino-diacetic acid
HNPCC	hereditary nonpolyposis colorectal cancer
I&D	incision and drainage
IBD	inflammatory bowel disease
IPAH	idiopathic pulmonary arterial hypertension
IPF	idiopathic pulmonary fibrosis
IUGR	intrauterine growth restriction
IVC	inferior vena cava
IVIG	intravenous immune globulin
LAR	low anterior resection
LBO	large bowel obstruction
LCIS	lobular carcinoma in situ
LES	lower esophageal sphincter
LGIB	lower gastrointestinal bleed
LLQ	left lower quadrant
LMWH	low molecular weight heparin
LUQ	left upper quadrant
LVRS	lung volume reduction surgery
MALT	mucosa-associated lymphoid tissue
MBP	mechanical bowel preparation
MEN	multiple endocrine neoplasia
MIBG	metaiodobenzylguanidine
MIS	minimally invasive surgery
MRCP	magnetic resonance cholangiopancreatography
MSAFP	maternal serum α-fetoprotein
NET	neuroendocrine tumour
NS	normal saline
OCP	oral contraceptive pill
OGD	oesophagogastroduodenoscopy
PMN	polymorphonuclear neutrophils
POD	postoperative day
PPI	proton pump inhibitor
PTC	percutaneous transhepatic cholangiography
PTT	partial thromboplastin time
PUD	peptic ulcer disease
RAI	radioactive iodine
RL	Ringer's lactate
RLQ	right lower quadrant
RUQ	right upper quadrant
SBO	small bowel obstruction
SBFT	small bowel follow-through
SCC	squamous cell carcinoma
SIADH	syndrome of inappropriate anti-diuretic hormone
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SNLB	sentinel lymph node biopsy
TED	thromboembolic deterrent
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
UC	ulcerative colitis
UGI	upper gastrointestinal series
UGIB	upper gastrointestinal bleed
URTI	upper respiratory tract infection
VATS	video-assisted thoracoscopic surgery
VIP	vasoactive intestinal peptide
VTE	venous thromboembolism

Basic Anatomy Review

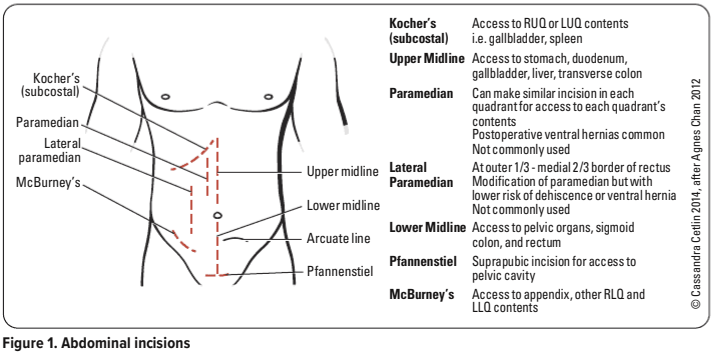
Kocher's (subcostal)
Paramedian
Lateral paramedian
McBurney's
Upper midline
Lower midline
Arcuate line
Pfannenstiel
Kocher's (subcostal) Access to RUQ or LUQ contents i.e. gallbladder, spleen
Upper Midline Access to stomach, duodenum, gallbladder, liver, transverse colon
Paramedian Can make similar incision in each quadrant for access to each quadrant's contents
Postoperative ventral hernias common
Not commonly used
Lateral Paramedian At outer 1/3 - medial 2/3 border of rectus
Modification of paramedian but with lower risk of dehiscence or ventral hernia
Not commonly used
Lower Midline Access to pelvic organs, sigmoid colon, and rectum
Pfannenstiel Suprapubic incision for access to pelvic cavity
McBurney's Access to appendix, other RLQ and LLQ contents
© Cassandra Cetlin 2014, after Agnes Chan 2012

Figure 1. Abdominal incisions

Lateral Abdominal Wall Layers and their Continuous Spermatic and Scrotal Structures (superficial to deep)

1. skin (epidermis, dermis, subcutaneous fat)
2. superficial fascia
   - Camper's fascia (fatty) → Dartos muscle/fascia
   - Scarpa's fascia (membranous) → Colles' superficial perineal fascia
3. muscle (see *Figure 2 and Figure 3, GS3*)
   - external oblique → inguinal ligament → external spermatic fascia
   - internal oblique → cremasteric muscle/fascia
   - transversus abdominis → posterior inguinal wall
4. transversalis fascia → internal spermatic fascia
5. preperitoneal fat
6. peritoneum → tunica vaginalis

Midline Abdominal Wall Layers (superficial to deep)

1. skin
2. superficial fascia
3. rectus abdominis muscle: in rectus sheath, divided by linea alba (see *Figure 3, GS3*)
   - above arcuate line (midway between symphysis pubis and umbilicus)
     - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
     - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus abdominis aponeurosis
   - below arcuate line
     - aponeuroses of external oblique, internal oblique, and transversus abdominis all pass in front of rectus abdominis

4. arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle (superficial to posterior rectus sheath above arcuate line)
5. transversalis fascia
6. peritoneum

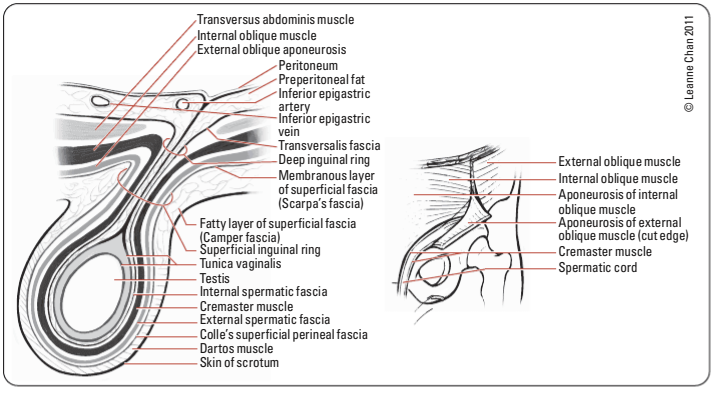

Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord

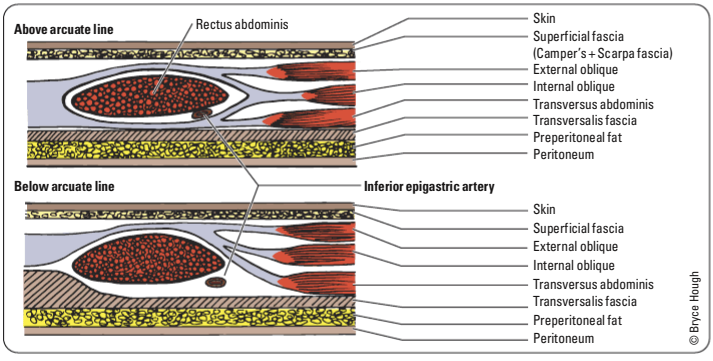

Figure 3. Midline cross-section of abdominal wall

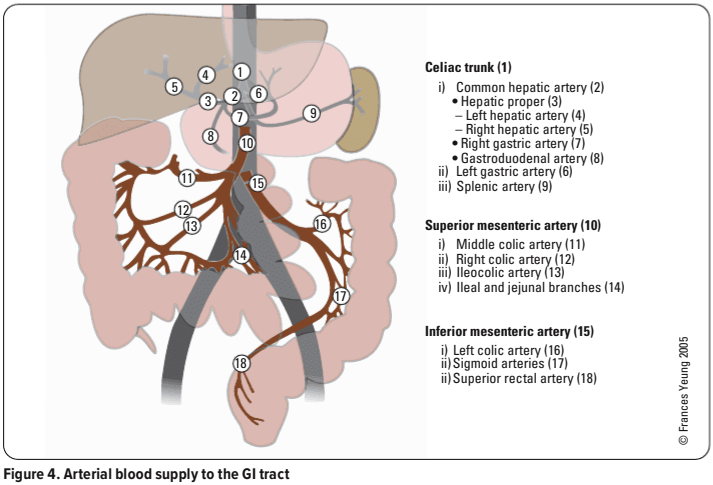
Celiac trunk (1)
i) Common hepatic artery (2)
• Hepatic proper (3)
– Left hepatic artery (4)
– Right hepatic artery (5)
• Right gastric artery (7)
• Gastroduodenal artery (8)
ii) Left gastric artery (6)
iii) Splenic artery (9)
Superior mesenteric artery (10)
i) Middle colic artery (11)
ii) Right colic artery (12)
iii) Ileocolic artery (13)
iv) Ileal and jejunal branches (14)
Inferior mesenteric artery (15)
i) Left colic artery (16)
ii) Sigmoid arteries (17)
iii) Superior rectal artery (18)
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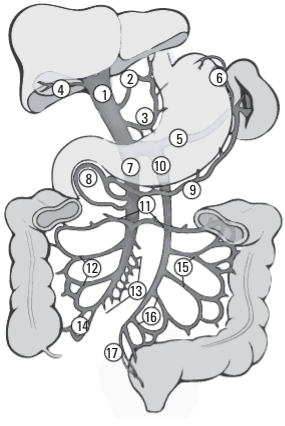
Figure 4. Arterial blood supply to the GI tract

Organ	Arterial Blood Supply
Liver	Left and right hepatic (branches of hepatic proper)
Spleen	Splenic
Gallbladder	Cystic (branch of right hepatic)
Stomach	Lesser curvature: right and left gastric Greater curvature: right (branch of gastroduodenal) and left (branch of splenic) gastroepiploic Fundus: short gastrics (branches of splenic)
Duodenum	Gastroduodenal Pancreaticoduodenals (superior branch of gastroduodenal, inferior branch of superior mesenteric)
Pancreas	Pancreatic branches of splenic Pancreaticoduodenals
Small intestine	Superior mesenteric branches: jejunal, ileal, ileocolic
Large intestine	Superior mesenteric branches: right colic, middle colic Inferior mesenteric branches: left colic, sigmoid, superior rectal

Venous Flow



Portal vein (1)

Superior mesenteric vein (7)

i) Ileal and jejunal veins (13)
ii) Ileocolic vein (14)
iii) Right colic vein (12)
iv) Middle colic vein (11)
v) Pancreaticoduodenal vein (8)
vi) Right gastroepiploic vein (9)

Splenic vein (5)

i) Inferior mesenteric vein (10) (superior rectal vein until crossing common iliac vessels)
- Left colic veins (15)
- Sigmoid veins (16)
- Superior rectal veins (17)

ii) Pancreatic veins
iii) Left gastroepiploic vein
iv) Short gastric veins (6)

Left gastric (coronary) vein (2)

Right gastric vein (3)

Cystic vein (4)

Paraumbilical vein – (within round ligament, not shown)

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Figure 5. Venous drainage of the GI tract

Differential Diagnoses of Common Presentations

Acute Abdominal Pain

- acute abdomen = severe abdominal pain of acute onset and requires urgent medical attention
- in patients with acute abdominal pain, the first diagnoses that you should consider are those requiring potential urgent surgical intervention, including:
  - peritonitis
  - bowel obstruction

Table 1. Differential Diagnosis of Acute Abdominal Pain

Right Upper Quadrant (RUQ)	Right Lower Quadrant (RLQ)
Hepatobiliary	**Gastrointestinal**
Biliary colic	Appendicitis*
Cholecystitis*	Crohn's disease
Cholangitis	Tuberculosis of the ileocecal junction
CBD obstruction (e.g. stone, tumour)	Cecal tumour
Hepatitis (includes perihepatitis/Fitz-Hugh-Curtis syndrome)	Intussusception
Gastrointestinal	Mesenteric lymphadenitis (Yersinia)
Pancreatitis	Cecal diverticulitis
Presentation of gastric, duodenal, or pancreatic pathology	Cecal volvulus*
Hepatic flexure pathology (e.g. CRC, subcostal incisional hernia)	Hernia: femoral, inguinal obstruction, Amyand's (and resulting cecal distention)
Genitourinary	**Gynecological**
Nephrolithiasis*	See 'suprapubic'
Pyelonephritis	**Genitourinary**
Renal: mass, ischemia, trauma	See 'suprapubic'
Cardiopulmonary	**Extraperitoneal**
Right lower lobe pneumonia	Abdominal wall hematoma/abscess
Effusion/empyema	Psoas abscess
CHF (causing hepatic congestion and right pleural effusion)	
MI	
Pericarditis	
Pleuritis	
Miscellaneous	
Herpes zoster	
Trauma	
Costochondritis (Infectious*)	

*indicated need for urgent surgical evaluation

In All Patients Presenting with an Acute Abdomen, Order the Following:
Key Tests for Specific Diagnosis
- ALP, ALT, AST, bilirubin
- Lipase/ amylase
- Urinalysis
- β-hCG (in women of childbearing age)
- Troponins
- Lactate

Key Tests for OR Preparation
- CBC, electrolytes, creatinine, glucose
- INR/PTT
- CXR (if history of cardiac or pulmonary disease)
- ECG if clinically indicated by history or if >69 yr and no risk factors

Note: Choosing Wisely does not recommend routine preoperative blood work for ambulatory/elective surgery

Types of Peritonitis

Primary peritonitis: spontaneous without clear etiology

Secondary peritonitis: due to a perforated viscus

Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

Localization of Pain

Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation; kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain

Parietal peritoneum: supplied by somatic sensory nerves of body wall. Pain is sharp and well-localized

Visceral peritoneum: supplied by autonomic sensory fibres. Pain is colicky and poorly localized

Table 1. Differential Diagnosis of Acute Abdominal Pain

Left Upper Quadrant (LUQ)	Left Lower Quadrant (LLQ)
Pancreatic Pancreatitis (acute vs. chronic) Pancreatic pseudocyst Pancreatic tumours*	**Gastrointestinal** Diverticulitis* Diverticulosis Colon/sigmoid/rectal cancer Fecal impaction Proctitis (e.g. UC, infectious; i.e. gonococcus or *Chlamydia*) Sigmoid volvulus*
Gastrointestinal Gastritis PUD Splenic flexure pathology (e.g. CRC, ischemia)	Hernia (incarcerated/strangulated*)
Splenic Splenic infarct/abscess* Splenomegaly Splenic rupture* Splenic artery aneurysm	**Gynecological** See 'suprapubic'
Cardiopulmonary (see RUQ and Epigastric)	**Genitourinary** See 'suprapubic'
Genitourinary (see RUQ)	**Extraperitoneal** Abdominal wall hematoma/abscess* Psoas abscess
	See Gynecology, Urology, Respirology, and Cardiology and Cardiac Surgery for further details regarding respective etiologies of acute abdominal pain

EPIGASTRIC	SUPRAPUBIC	DIFFUSE
Cardiac Aortic dissection/ruptured AAA* MI Pericarditis	**Gastrointestinal (see RLQ/LLQ)** Acute appendicitis* IBD	**Gastrointestinal** Peritonitis* Early appendicitis, perforated appendicitis* Mesenteric ischemia* Gastroenteritis/colitis Constipation Bowel obstruction* Pancreatitis IBD Irritable bowel syndrome Ogilvie's syndrome
Gastrointestinal Gastritis GERD/esophagitis PUD Pancreatitis Mallory-Weiss tear	**Gynecological** Ectopic pregnancy* Pelvic inflammatory disease Endometriosis Threatened/incomplete abortion* Hydrosalpinx/salpingitis Ovarian torsion* Hemorrhagic fibroid Tubo-ovarian abscess Gynecological tumours	**Cardiovascular/Hematological** Aortic dissection* Ruptured AAA* Sickle cell crisis
	Genitourinary Cystitis (infectious, hemorrhagic) Hydroureter/urinary colic Epididymitis Testicular torsion* Acute urinary retention	**Genitourinary/Gynecological** Perforated ectopic pregnancy* Pelvic inflammatory disease Acute urinary retention
	Extraperitoneal Rectus sheath hematoma	**Endocrinological** Carcinoid syndrome* Diabetic ketoacidosis Addisonian crisis Hypercalcemia
		Other Lead poisoning Tertiary syphilis

*indicated need for urgent surgical evaluation

Referred Pain

Biliary colic: to right shoulder or scapula

Renal colic: to groin

Appendicitis: periumbilical to RLQ

Pancreatitis: to back

Ruptured AAA: to back or flank

Perforated ulcer: to RLQ (right paracolic gutter)

Hip pain: to groin

Ovarian torsion: to flank or groin

Most Common Presentations of Surgical Pain

Sudden onset with rigid abdomen = perforated viscus

Pain out of proportion to physical findings = ischemic bowel

Vague pain that subsequently localizes = appendicitis or other intra-abdominal process that irritates the parietal peritoneum

Waves of colicky pain = bowel obstruction

Acute Abdominal Pain Mnemonic

ABDOMINAL
Appendicitis
Biliary tract disease
Diverticulitis
Ovarian disease
Malignancy
Intestinal obstruction
Nephritic disorders
Acute pancreatitis
Liquor/ethanol

Abdominal Mass

Table 2. Differential Diagnosis of Abdominal Mass

RUQ	Upper Midline	LUQ
Gallbladder: cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis **Biliary tract:** Klatskin tumour Liver: hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)	**Pancreas:** pancreatic adenocarcinoma, other pancreatic neoplasms, pseudocyst **Abdominal aorta:** AAA (pulsatile) **GI:** gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma	**Spleen:** splenomegaly, tumour, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly **Stomach:** tumour
RLQ	**Lower Midline**	**LLQ**
Intestine: stool, tumour (CRC), mesenteric adenitis, appendicitis, appendiceal phlegmon or other abscess, typhlitis, intussusception, Crohn's inflammation **Ovary:** ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, Krukenberg) **Fallopian tube:** ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour	**Uterus:** pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra **GU:** bladder distention, tumour	**Intestine:** stool, tumour, abscess (see RLQ) **Ovary:** see RLQ **Fallopian tube:** see RLQ

Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate surgical intervention

Gastrointestinal Bleeding

- see Gastroenterology, G28 and G30

Indications for Surgery

- failure of medical management (after at least 2 endoscopic attempts at management)
- exsanguinating hemorrhage: hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage with up to two attempts of endoscopic hemostasis
- prolonged bleeding with transfusion requirement >3 units
- bleeding at rate >1 unit/8h

Indications for Urgent Operation

IHOP
Ischemia
Hemorrhage
Obstruction
Perforation

Surgical Management of GI Bleeding

- UGIB
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia), may present with anemia, hypovolemic shock
  - initial management with PPIs and endoscopy; if fails, then consider surgical management appropriate to etiology
  - PUD accounts for approximately 55% of severe UGIB
- LGIB
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon, rarely melena (right-sided colonic bleeding)
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - 75% of patients will spontaneously stop bleeding, however if bleeding continues, barium enema should NOT be performed
  - angiography or RBC scan to determine source as indicated
  - surgery indicated if bleeding is persistent - aimed at resection of area containing source of bleeding
  - for obscure bleed conduct wireless capsule endoscopy, may require blind total colectomy if the source is not found
  - diverticular bleeding is the most common cause of LGIB (accounting for 40% of cases)

Overt Bleeding: obvious hematemesis, hematochezia or melena per rectum (i.e. visible to naked eye)
Occult Bleeding: bleeding per rectum is not obvious to naked eye (e.g. positive guaiac FOBT)
Obscure Bleeding: bleeding with no identifiable source after colonoscopy and endoscopy (source usually in small bowel). Can be either overt or occult

Table 3. Differential Diagnosis of GI Bleeding

Anatomical Source	Etiology	
Hematological	Excess anticoagulation (warfarin, heparin, etc.) Excess antiplatelet (clopidogrel, ASA)	DIC Congenital bleeding disorders
Nose	Epistaxis	
Esophagus	Esophageal varices Mallory-Weiss tear Esophagitis	Aorto-esophageal fistula (generally post endovascular aortic repair)* Esophageal cancer
Stomach	Gastritis Gastric varices Dieulafoy's lesion	Gastric ulcer Gastric cancer*
Duodenum	Duodenal ulcer Perforated duodenal ulcer*	Duodenal cancer*
Jejunum	Tumours* Polyps Ulcers	
Ileum and Ileocecal Junction	Meckel's diverticulum Small bowel obstruction	Crohn's disease* Tuberculosis of ileocecal junction
Large Intestine	Colorectal cancer* Mesenteric thrombosis/ischemic bowel* UC* (subtotal colectomy if failure of medical management) Angiodysplasia Diverticulosis (*if bleeding is persistent)	Crohn's disease (less frequently presents with bleeding)* Pancolitis (infectious, chemotherapy, or radiation induced) Bleeding post-gastrointestinal anastomosis
Sigmoid	Diverticulosis (*if bleeding is persistent) Sigmoid cancer* Bleeding post-polypectomy	Polyps (*if not amenable to colonoscopic polypectomy) IBD
Rectum and Anus	Hemorrhoids Fissures Rectal cancer* Anal varices	Polyps (*if not amenable to colonoscopic polypectomy) Crohn's or UC* Solitary rectal ulcer syndrome

*Managed surgically in most cases

Bloodwork for GI Bleeds
CBC (including platelet count), serum chemistries (electrolytes, BUN, LFTs, etc.), coagulation studies (INR, PT, PTT), blood type and crossmatch if anticipate transfusion

Jaundice

- see Gastroenterology, G45

Biochemical Signs for Differentiating Jaundice
Hepatocellular: Elevated bilirubin + elevated ALT/AST
Cholestatic: Elevated bilirubin + elevated ALP/GGT ± duct dilatation upon biliary U/S
Hemolysis: ↓ haptoglobin ↑ LDH

Note: cholestatic jaundice is often surgical

Preoperative Preparations

Considerations

- informed consent (see Ethical, Legal, and Organizational Medicine, ELOM12)
- screening questionnaire to determine risk factors e.g. age, exercise capacity, medication use, allergies, exposure to people with infection (i.e. COVID-19)
- consider preoperative anesthesia, medicine consult as indicated to optimize patient status
- NPO according to fasting guidelines (see Anesthesia, A5)
- IV-balanced crystalloid at maintenance rate (4:2:1 rule for paediatrics, roughly 100-125 cc/h for adults): NS or RL (RL most common); bolus to catch up on estimated losses including losses from bowel prep
  - appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patients can take their regular medications except for hypoglycemic agents, diuretics, and ACEis
- patients with primary adrenal insufficiency (e.g. Addison's disease) or secondary adrenal insufficiency (e.g. glucocorticoid use) may require additional glucocorticoid stress dose coverage
- anticoagulation/antiplatelet medication must be managed to decrease surgical bleeding but not put patient at risk for increased thrombotic events (e.g. Bridging: switching from warfarin to LMWH, easier to start/stop as needed)
- prophylactic antibiotics depending on wound class (immediately/within 1 h prior to incision): cefazolin (skin flora coverage) ± metronidazole (GI flora coverage) for contaminated cases
- role of MBP: Current evidence suggests that use of MBP preoperatively has no impact on postoperative complications, and therefore, routine use of MBP for non-LAR elective colorectal surgery is not recommended
  - MBP is indicated in open or laparoscopic anterior resection i.e. rectal resection where anastomosis is at or below sacral promontory; given with antibiotics
- assess risk for postoperative VTE prior to surgery based on procedure- and patient-related factors; tools such as Caprini Score can be used
  - only hold VTE prophylaxis if epidural is expected
- smoking cessation and weight loss preoperatively can significantly decrease postoperative complications
- infection: delay elective surgery until infection managed, including respiratory infection (particularly in asthma patients)
- when scheduling elective surgeries following a COVID-19 diagnosis, consider the severity of COVID-19 illness, the risks of complications, and risks of delaying surgery

Table 4. Recommendations for Timing of Surgery following Recovery from COVID-19 with Consideration of Individual Risk/Benefits

Priority of Surgical Procedure	Clinical Severity of COVID-19 Infection			
	Mild	Moderate	Severe	Critically ill
	Mild (suspected or confirmed) COVID-19 and/or asymptomatic and/or upper respiratory tract infection	Moderate symptomatic COVID-19 not requiring hospitalization and/or persistent symptoms	Lung involvement requiring hospitalization and/or significant comorbidities and/or immunocompromised	Severe COVID-19 with ICU admission and/or meet criteria for severe disease and/or severely immunocompromised
Urgent or Emergent <2 wk ACATS and PCATS Urgent within 3, 7 or 14 d	Do case urgently/ emergently	Do case urgently/ emergently	<7 wk post-infection consider non-operative options if safe and available	<7 wk post-infection consider non-operative options if safe and available
Urgent (28 or 42 d) 2-6 wk ACATS/PCATS	4 -7 wk post infection	7 wk post infection	7 wk post infection	12 wk post infection
Elective (>43 d) >6 wk ACATS/PCATS				

Investigations

- see Anesthesia, A4
- routine preoperative laboratory investigations for elective procedures should be selective
  - only ASA class and surgical risk have been found to independently predict postoperative adverse effects
- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, creatinine
- INR/PT, PTT
- CXR (PA and lateral) for patients with history of cardiac or pulmonary disease
- ECG as indicated by history or age>69 and no risk factors
- β-hCG testing in all women of reproductive age
- for patients undergoing low-risk surgery without systemic disease (ASA I or II), routine preoperative chest x-rays, CBC, INR, and PTT should be avoided

Bilirubin Levels

	Pre-hepatic	Intra-hepatic	Post-hepatic
Serum Bilirubin			
Indirect	↑	↑	N
Direct	N	↑	↑
Urine			
Urobilinogen	↑	↑	–
Bilirubin	–	+	+
Fecal			
Urobilinogen	↑	↑	–

In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out

Surgical Emergencies: Take an AMPLE History

Allergies
Medications
Past medical/surgical history (including anesthesia and bleeding disorders)
Last meal
Events – HPI

Best Practice in General Surgery (BPIGS)
http://www.bpigs.ca/
Best Practice in Surgery is a resource from the quality improvement program at the University of Toronto Department of Surgery. Since its inception, it has expanded beyond general surgery best practices and provides EBM guidelines for a variety of fields and procedures

Mechanical Bowel Preparation Strategies: A Clinical Practice Guideline developed by the University of Toronto's Best Practice in Surgery
Informed by: Can J Surg 2010;53:385-395
14 RCTs (5071 participants), 8 meta-analyses
1. All open/laparoscopic colorectal procedures (excluding LARs ± diverting stoma)
   - No MBP
   - No dietary restrictions before NPO
   - Fleet enema for left colon anastomoses with transrectal stapling
2. Open/laparoscopic LAR ± diverting stoma
   - MBP
   - No dietary restrictions before MBP; clear fluids after MBP complete

Drains

- NG tube
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding, and/or administration of medications, if necessary
  - 2 types: NG tube (for drainage or feeding) and Dobhoff (for feeding only)
  - insertion should be done in stages with x-ray protocol to avoid injury
  - contraindications: suspected basal skull fracture, obstruction of nasal passages, esophageal stricture, esophageal varices
- Foley catheter with urometer
  - indications: to accurately monitor urine output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  - contraindications: suspected urethral injury and difficult insertion of catheter

Drain Size
Measured by the unit French:
French = diameter (mm) x 3

Surgical Complications

- general principles in preventing complications during the postoperative period include:
  - frequent examination of the patient (daily or more) and their wound
  - removal of surgical tubes as soon as possible (e.g. Foley catheters and surgical drains)
  - early mobilization
  - monitor fluid balance and electrolytes
  - analgesia - enough to adequately address pain (minimize opioids through routine use of anti-inflammatories and acetaminophen)

Postoperative Fever

- postoperative fever is considered a temperature higher than 38°C on two consecutive postoperative days or higher than 39°C on any postoperative day
- fever does not necessarily imply infection, particularly in the first 24-48 h postoperatively
- fever may not be present or may be blunted if patient is receiving chemotherapy, glucocorticoids, or other immunosuppressive agents
- timing of fever may help identify cause
- hours after surgery - POD #1
    - inflammatory reaction in response to physiological stress from surgery; most common cause of fever on POD #1-3 and unlikely to be infectious (unless necrotizing fasciitis or another severe infection)
    - reaction to blood products received during surgery
    - malignant hyperthermia
  - POD #1-2 (acute)
    - atelectasis
    - early necrotizing fasciitis wound infection (especially *Clostridium perfringens*, β-hemolytic Group A *Streptococcus*); feel for crepitus and look for "dishwater" drainage
    - aspiration pneumonitis
    - other: acute adrenal insufficiency, thyroid storm, and transfusion reaction
  - POD #3-7: likely infectious
    - UTI, surgical site infection, IV site/line infection (commonly with *Staphylococcus*), septic thrombophlebitis, and leakage at bowel anastomosis (tachycardia, hypotension, oliguria, and abdominal pain)
  - POD #8+
    - intra-abdominal abscess, DVT/PE (can be anytime postoperative, most commonly POD #8-10, may occur earlier but recognition is often delayed), and drug fever
    - other: URTI, infected seroma/biloma/hematoma, *C. difficile* colitis, and endocarditis

Treatment

- resuscitation then treat primary cause

Wound/Incisional Complications

WOUND CARE (see Plastic Surgery, PL8)

- can shower POD #2-3 after epithelialization of wound (or earlier depending on dressing)
- most dressings can be removed POD #2 and left uncovered if dry
- Steri strips or dermabond glue should be left on for up to 2 wk
- examine wound for wet dressing, signs of infection (fever, tachycardia, and pain)
- skin sutures and staples can be removed POD #7-10
  - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, or immunosuppressed) removed POD #14 or earlier if there are signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin or ulcer)

DRAINS

- drains may be placed selectively at the time of surgery to prevent fluid accumulation (blood, pus, serum, bile, and urine)
  - can be used to assess quantity of third space fluid accumulation postoperatively
- potential route of infection; to decrease risk of wound infection bring out through separate incision (vs. operative wound) and remove as soon as possible
- types of drains
  - open (e.g. Penrose), higher risk of infection
  - closed: 1) gravity drainage (e.g. Foley catheter); 2) underwater-seal drainage system (e.g. chest tube); 3) suction drainage (e.g. Jackson-Pratt)
  - sump (e.g. NG tube)
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually <30-50 cc/24 h)
- drains do not guarantee that the patient will not form a collection of fluid
- ridged drains can erode through internal structures, and excessive suction can cause necrosis
- evidence does not support routine postoperative drainage of abdominal cavity

SURGICAL SITE INFECTION

Etiology

- most surgical wounds are contaminated by bacteria often consisting of normal endogenous flora from skin, respiratory, GU, or GI tracts (depending on surgery)
  - e.g. skin flora (Gram positive cocci: *S. aureus, Streptococcus* spp.) and GI flora (Gram-positive microbes: *Enterococcus* spp., Clostridium spp.; Gram-negative rods: *E. coli*; anaerobic species)

Risk Factors

Table 5. Classification of Surgical Wound Contamination

Classification	Clean	Clean-Contaminated	Contaminated	Dirty/Infected
Definition	Incision under sterile conditions; nontraumatic; no entrance of hollow organ	Incision under sterile conditions; ENTRANCE of hollow viscus with no spillage; no evidence of active infection; minimal contamination with no spillage	Incision under sterile conditions; MAJOR contamination of wound during procedure (i.e. gross spillage of stool, infection in biliary, respiratory, or GU systems)	Established infection present before wound is made in skin; traumatic wound with delayed treatment Traumatic wound with delayed treatment
Example	Hernia repair	Routine cholecystectomy; colon resection	Bowel obstruction with enterotomy and spillage of contents; necrotic bowel resection; fresh traumatic wounds	Appendiceal abscess; traumatic wound with contaminated devitalized tissue; perforated viscus
Infection Rate	<2%	3-4%	7-10%	30-40%
Wound Closure	Primary closure	Primary closure	Often secondary closure	Secondary closure

- patient characteristics
  - age, DM, steroids, immunosuppression, smoking, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, and chemotherapy
- other factors
  - prolonged preoperative hospitalization, skin preparation, multiple antibiotics, reduced blood flow, break in sterile technique, foreign bodies (drains, sutures, grafts), excessive tension, hematoma, seroma, hypoxemia, and hypothermia

Prophylaxis

- preoperative antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamicin or vancomycin)
  - within 1 h pre-incision; can re-dose at 1-2 half-lives (~q4-8 h) in the OR
  - not required for low-risk or clean surgery, e.g. elective thyroidectomy, cholecystectomy, hemorrhoidectomy, fistulotomy, and sphincterotomy for fissure
  - important to review patient factors and clinical context; immunosuppression (transplant, Cushing's, malignancy, etc.) would likely warrant preoperative antibiotics
  - some evidence suggests role in breast surgery
  - important that redosing antibiotics is performed if surgery is longer than the half-life of antibiotics
- reserve postoperative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C in the OR)
- hyperoxygenation (consider FiO_2 of 80% in OR)
- chlorhexidine-alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving done at the time of surgery
- consider delayed primary closure of incision for contaminated wounds
- use sterile closing tray for laparotomy

Clinical Features

- typically fever POD #5-8 (*Streptococcus* and *Clostridium* can present in 24 h)
- localized pain, blanchable erythema, induration, purulent discharge, and warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, and hernia

Complication	Laboratory/Imaging Tests
Wound Complication	Wound culture, CBC, CT scan
Fever	CBC, electrolytes, glucose, creatinine, BUN, U/A, CXR, urine/blood/sputum and wound culture if applicable
Respiratory Distress	EKG, echo, CXR, ABG, CT-angiography of the chest
AKI/Oliguria	Electrolytes, glucose, creatinine, BUN, U/A with microscopy, urine electrolytes, EKG, renal U/S
Hypotension	CBC, electrolytes, glucose, creatinine, BUN, lactate, ABG, ACTH stimulation testing, cortisol level, and coagulation studies
Ileus	Electrolytes, glucose, creatinine, BUN, AXR
Stress Ulcer	CBC, upper endoscopy

Preoperative Skin Antiseptics for Preventing Surgical Wound Infections after Clean Surgery
Cochrane DB Syst Rev 2015;4:CD003949
Purpose: To determine whether preoperative skin antisepsis prior to clean surgery prevents surgical-site infection (SSI) and to compare the effectiveness of other antiseptics.
Methods: Systematic review of RCTs part of the Cochrane Wounds Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL). Main outcome was SSI. Secondary outcomes included quality of life, mortality, and resource use.
Results: 13 RCTs (n=2623 patients) were included that made 11 total comparisons between skin antiseptics. A single study found that 0.5% chlorhexidine solution in methylated spirits was significantly superior in preventing SSIs after clean surgery compared to alcohol-based povidone iodine solution. No other statistically significant differences were found.
Conclusions: Further research is warranted to determine the effectiveness of one antiseptic over the others at preventing SSI post clean surgery.

Primary vs. Delayed Primary Incision Closure in Contaminated Abdominal Surgery: A Meta-Analysis
J Surg Res 2019;239:22-30
Purpose: To determine if delayed primary incision closure (DPC) has lower rates of surgical site infections (SSI) and length of stay (LOS) compared to primary incision closure (PC) in contaminated abdominal surgery.
Methods: Systematic review and meta-analysis of RCTs in Medline, Embase, and Cochrane database between 1980-2017.
Results: 12 RCTs were included and analyzed. Using a fixed-effect model, DPC showed significantly reduced SSI with risk ratio of 0.64 (95% CI 0.51-0.79; P<0.0001) and reduced LOS with a mean difference of less than one day compared with PC. However, using a random-effect model, there was no significant difference in SSI or LOS.
Conclusions: DPC may be the preferential option in contaminated abdominal incisions, however higher quality research is required to provide a more comprehensive evidence base.

Treatment
- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- reopen affected part of incision, drain, pack, heal by secondary intention in most cases
- for deeper or necrotizing infections, debride necrotic and non-viable tissue
- antibiotics and demarcation of erythema only if cellulitis or immunodeficiency

WOUND HEMORRHAGE/HEMATOMA

Risk Factors
- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial HTN, and severe cough
- more common with transverse incisions through muscle due to vascularity of muscle
- more clinically relevant in small working spaces such as breast or thyroid surgery (airway edema/compression)

Clinical Features
- pain, swelling, discolouration of wound edges, and leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency: consider having a suture kit at bedside in all neck surgery in the event of having to open the wound emergently (most important treatment in this case is to protect the airway with intubation)

Treatment
- pressure dressing
- open drainage ± wound packing (large hematoma only)
- if significant bleeding, may need to re-operate to find source (often do not find a discrete source)

SEROMA
- fluid collection related to serous lymph drainage
- secondary to transection of lymph vessels
- increased infection risk if drained

Treatment
- observation
- consider pressure dressing ± needle drainage (this may increase infection risk)

WOUND DEHISCENCE
- disruption of a wound that was primarily closed, causing loss of barrier of skin or fascia

Risk Factors
- local: technical failure of closure, excessive tension on the wound, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, and transverse incision
- systemic: male, smoking, malnutrition (hypoalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, others (e.g. age, sepsis, and uremia)
- DM alone is not a risk factor
- when removing staples, those at high risk should have alternate staples removed first in a small area to ensure the fascia is intact before removing more (PRO TIP)

Clinical Features
- typically POD #1-3 or #7-10; most common presentation sign is serosanguinous (salmon-coloured) drainage from wound; erythema or leakage of enteric material
- ± evisceration
- palpation of wound edge: should normally feel a "healing ridge" from abdominal wall closure (raised area of tissue under incision)

Treatment
- place moist dressing over wound with binder around abdomen and transfer to OR
- may consider conservative management with debridement of fascial and/or skin margins
- evisceration (i.e. 'burst abdomen') is a surgical emergency: take patient for operative re-closure

INCISIONAL HERNIA
- a late complication of fascial dehiscence and failure of fascial closure; GI contents are still contained within sack of peritoneum
  - hernia can develop 6-8 wk postoperatively due to poor wound healing and/or increased stress on abdominal wall
- symptoms aggravated by coughing or straining
- smaller fascial defects such as laparoscopic port sites have a higher risk of incarceration
- definitive treatment: surgical repair
  - large hernias that pose little risk of incarceration do not need to be repaired as minimal chance of bowel obstruction

Small Bites vs. Large Bites for Closure of Abdominal Midline Incisions (Stitch): A Double-Blind, Multicentre, Randomised Controlled Trial
Lancet 2015;386:1254-1260
Purpose: To compare the large bites suture technique with the small bites technique for fascial closure of midline laparotomy incisions.
Methods: RCT conducted at 10 hospitals in the Netherlands. Patients undergoing elective abdominal surgery randomized (1:1) to small or large bite technique. Primary outcome was incisional hernia occurrence.
Results: At one year follow-up, the large bites group had a greater incidence of incisional hernia occurrence than the small bites group (21% vs. 13%, respectively). Rates of adverse events did not differ between the groups.
Conclusion: Small bites suture technique is superior to the large bites technique for prevention of incisional hernia in midline incisions and is not associated with a higher rate of adverse events.

Urinary and Renal Complications

URINARY RETENTION
- may occur after any operation with general anesthesia or more commonly with spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia and patients on anticholinergics but can also happen in young, healthy patients

Clinical Features
- abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL

Treatment
- in-and-out catheter to rest bladder, then trial of voiding
- often accompanied by an α-blocker such as tamsulosin (does not start working for 48 h)
- if postoperative retention: patients may need to be sent home with foley catheter and leg-bag (urometer) to follow-up within the week for trial-of-void

OLIGURIA/ANURIA

Etiology
- prerenal (e.g. hypovolemia due to transient renal hypoperfusion) vs. renal (e.g. ATN, acute interstitial nephritis (AIN), acute glomerulonephritis) vs. postrenal (e.g. urinary tract obstruction)
- most common postoperative cause is prerenal ± ischemic ATN
  - external fluid loss: hemorrhage, dehydration, and diarrhea
  - internal fluid loss: third-spacing due to bowel obstruction and pancreatitis

Clinical Features
- urine output <0.5 cc/kg/h (e.g. <450 cc in 75 kg patient in 12 h), increasing Cr and BUN

Treatment
- according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

Postoperative Dyspnea

- see *Respiratory Complications* and *Cardiac Complications, GS12*

Etiology
- respiratory: atelectasis, pneumonia/pneumonitis, pulmonary embolism (PE), ARDS, asthma, and pleural effusion
- cardiac: MI, arrhythmia, and CHF
- inadequate pain control

Respiratory Complications

ATELECTASIS
- comprises 90% of postoperative pulmonary complications

Risk Factors
- COPD, smoking, obesity, and elderly persons
- upper abdominal/thoracic surgery, oversedation, significant postoperative pain, and poor inspiratory effort

Clinical Features
- postoperative atelectasis may be asymptomatic or present as low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, and tachypnea

Treatment
- preoperative prophylaxis
  - smoking cessation (best if >8 wk preoperative)
- postoperative prophylaxis
  - incentive spirometry, deep breathing exercise, chest physiotherapy, and intermittent positive-pressure breathing
  - short-acting neuromuscular blocking agents
  - minimize use of respiratory depressive drugs, and ensure adequate pain control, and early ambulation

PNEUMONIA/PNEUMONITIS
- may be secondary to aspiration of gastric contents during anesthetic induction or extubation causing a chemical pneumonitis

Risk Factors
- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NG tube, pregnancy, and seizure disorder
- non-aspiration: atelectasis, immobility, and pre-existing respiratory disease

Clinical Features
- productive cough and fever
- tachycardia, cyanosis, respiratory failure, and decreased LOC
- CXR: pulmonary infiltrate

Treatment
- prophylaxis: see atelectasis prophylaxis, preoperative NPO/NG tube, and rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- empiric IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. piperacillin-tazobactam, cefepime + metronidazole)

PULMONARY EMBOLUS

Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset dyspnea, pleuritic chest pain, tachycardia, and fever
- most commonly POD #8-10, but can occur anytime postoperatively, even after discharge
- diagnosis made by chest CT scan usually

Treatment
- initial treatment: IV heparin or subcutaneous LMWH, bridging to therapeutic anticoagulation is required for a minimum of 3 mo (usually 6 mo); for patients with cancer, or other risk factors for hypercoagulability, the duration of anticoagulation may be longer; severe cases may require endovascular thrombectomy and thrombolysis
- Greenfield (IVC) filter if contraindications to anticoagulation helps prevent worsening of PE
- prophylaxis: subcutaneous heparin (5000 units BID/TID; less preferred) or LMWH, compression stockings (TED™ Hose), and sequential compression devices

PULMONARY EDEMA

Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess fluid overload, left ventricular (LV) failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, and alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anesthesia

New onset "asthma" and wheezing in the elderly is cardiogenic until proven otherwise

Clinical Features
- shortness of breath, crackles at lung bases, and CXR abnormal

Treatment (LMNOP)
- **L**asix® (furosemide)
- **M**orphine (decreases symptoms of dyspnea, venodilator, and afterload reduction)
- **N**itrates (venodilator)
- **O**xygen + non-invasive ventilation
- **P**osition (sit patient up)

RESPIRATORY FAILURE

Clinical Features
- dyspnea, cyanosis, and evidence of obstructive lung disease
- earliest manifestations - tachypnea and hypoxemia (RR >25, PO_2 <60)
- pulmonary edema and unexplained decrease in SaO_2

Treatment
- ABCs, O_2, ± positive pressure ventilation, and intubation
- bronchodilators and diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO_2 >60, consider ARDS (see Respirology, R24)

Cardiac Complications

- abnormal ECGs common in postoperative period (compare to preoperative ECG)
- common arrhythmias: supraventricular tachycardia, atrial fibrillation (secondary to fluid overload, PE, and MI)

MYOCARDIAL INFARCTION
- see Cardiology and Cardiac Surgery, C9
- surgery increases risk of MI
- incidence
  - 0.5% in previously asymptomatic men ages >50
  - 40-fold increase in men ages >50 with previous MI

Risk Factors
- preoperative HTN, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intraoperative hypotension
- operations >3 h
- angina

Clinical Features
- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, and hypotension

Intra-Abdominal Abscess

Definition
- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

Etiology
- usually polymicrobial: Gram-negative bacteria, and anaerobes
  - consider Gram-positives if coexisting cellulitis

Risk Factors
- emergency surgery and contaminated OR
- GI surgery with anastomotic leak
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid redistribution occurs

Clinical Features
- manifests at least 5-7 d after surgery. Cannot manifest earlier as it takes time to form collection
- persistent spiking fever, dull pain, and weight loss
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised and elderly)
- coexisting effusion (pleural effusion with subphrenic abscess)
- mass is often difficult to palpate
- common sites if disseminated peritonitis: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac or local peritonitis: peri-appendiceal, post-surgical anastomosis, diverticular, and psoas

Investigations
- CBC, blood cultures x2
- CT ± IV and water-soluble contrast
- C&S from drain

Treatment
- drain placement by interventional radiology (preferred), laparoscopy, and open drainage
- subsequent antibiotic coverage; ceftriaxone + metronidazole or piperacillin-tazobactam (Pip-Tazo)

Paralytic Ileus

- see *Paralytic Ileus, GS31*

Delirium

- see Psychiatry, PS23 and Neurology, N21

Thoracic and Foregut Surgery

Approach to the Solitary Pulmonary Nodule

- see Medical Imaging, MI8

Definition
- lesion up to 3 cm, which may or may not be calcified and is surrounded by normal lung
- can be benign or malignant

Differential Diagnosis of Upper GI Symptoms

GI Causes	Non-GI Causes
Cholelithiasis	MI
Diverticulitis	Angina
Peptic ulcer	Pericarditis
Achalasia	
Pancreatitis	
GERD	
Gastritis	
Hiatus hernia	

Horner has a MAP of the Coast
A Pancoast tumour compresses the cervical sympathetic plexus causing Horner's syndrome:
Miosis
Anhydrosis
Ptosis

Differential of an Anterior Compartment Mass

4 Ts
Thymoma
Thyroid enlargement (goitre)
Teratoma
Tumours (lymphoma, parathyroid, angiomatous)

Table 6. Differential Diagnosis for Benign vs. Malignant Solitary Nodule

Benign (70%)	Malignant (30%)	
Infectious granuloma (histoplasmosis, coccidiomycosis, TB, atypical mycobacteria) - most common **Other infections** (bacterial abscess, PCP, aspergilloma) **Benign neoplasms** (hamartoma, lipoma, fibroma) **Vascular** (AV malformation, pulmonary varix) **Developmental** (bronchogenic cyst) **Inflammatory** (granulomatosis with polyangiitis, rheumatoid nodule, sarcoidosis, amyloidosis) **Other** (infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma)	**Bronchogenic carcinoma** Adenocarcinoma SCC Large cell carcinoma Small cell carcinoma Small cell lung cancer	**Metastatic lesions** Breast Head and neck Melanoma Colon Kidney Sarcoma Germ cell tumours

Investigations

- CXR: always compare with previous CXR
- CT and contrast-enhanced CT of thorax
- biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  - if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  - if a biopsy is non-diagnostic, whether to observe, re-biopsy, or resect will depend on the level of suspicion
- watchful waiting: repeat CT scan at 3, 6, 12 mo depending on nodule characteristics and patient risk
- PET scan can narrow the differential diagnosis

Table 7. CT Characteristics of Benign vs. Malignant Solitary Nodule

Parameters	Benign	Malignant
Size	Nodule (<3 cm)	Mass (>3 cm)
Borders	Smooth or lobulated	Irregular or spiculated
Features	Calcified pattern: diffuse, central, laminated, "popcorn" pattern if hamartoma, usually no cavitation; if cavitating, wall is smooth and thin, no other lung pathology	Usually not calcified; if calcified, pattern is eccentric, stippled, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy
Doubling Time	Doubles in <20 or >400 d	Doubles between 20 and 400 d

Table 8. Evaluation of a Solitary Pulmonary Nodule

SOLID NODULES			
Nodule Type	**Size <6 mm (<100 mm^2)**	**Size 6-8 mm (100-250 mm^2)**	**Size >8 mm (>250 mm^2)**
Single			
Low-Risk	No routine follow-up	CT at 6-12 mo, then consider CT at 18-24 mo	Consider CT a 3 mo, PET/CT or tissue sampling
High-Risk	Optional CT at 12 mo	CT at 6-12 mo, then at 18-24 mo	Consider CT a 3 mo, PET/CT or tissue sampling
Multiple			
Low-Risk	No routine follow-up	CT at 3-6 mo, then consider CT at 18-24 mo	CT at 3-6 mo, then consider CT at 18-24 mo
High-Risk	Optional CT at 12 mo	CT at 3-6 mo, then at 18-24 mo	CT at 3-6 mo then at 18-24 mo
SUBSOLID NODULES			
Nodule Type	**Size <6 mm (<100 mm^2)**	**Size ≥6 mm (>100 mm^2)**	
Single			
Ground Glass	No routine follow-up	CT at 6-12 mo to confirm persistence then CT every 2 yr until 5 yr	
Part Solid	No routine follow-up	CT at 3-6 mo to confirm persistence If unchanged and solid component remains <6 mm, annual CT should be performed for 5 yr	
Multiple	CT at 3-6 mo. If stable consider CT at 2 and 4 yr	CT at 3-6 mo Subsequent management based on the most suspicious nodule(s)	

Adapted from: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images. The Fleischner Society 2017. Radiology Journal. doi:10.1148/radiol.2017161659. Feb 23 2017.

Lung Cancer

Classification

- lung tumours can be classified as:
  - primary or secondary
  - benign or malignant
  - endobronchial or parenchymal
- bronchogenic carcinoma (epithelial lung tumours) are the most common type of primary lung tumour (other types make up less than 1%)
  - small cell lung cancer (SCLC): 10-15%

- non-small-cell lung cancer (NSCLC): 85-90%
  - SCC: arise from the proximal respiratory epithelium
  - adenocarcinoma: incidence is increasing; most common subtype in nonsmokers
    - mucinous adenocarcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring
  - large cell carcinoma
- benign epithelial lung tumours can be classified as papillomas or adenomas

Table 9. Characteristics of Lung Cancer

Cell Type	Percentage of Lung Cancer	Correlation with Smoking	Location	Histology	Metastasis	5 Yr Survival Rates
SCLC	10-15%	Strong	Central	Oat cell, neuroendocrine	Disseminated at presentation Origin in endobronchial cells	10-13% limited stage, 1-2% extensive stage
Adenocarcinoma	M: 35% F: 40%	Moderate	Peripheral	Papillary, lepidic, acinar, mucinous, solid	Early, distant	70% early stage, 7% advanced stage
SCC	30%	Strong	Central	Keratin, intercellular bridges	Local invasion and distant spread, may cavitate	47% early stage, 6% advanced stage
Large Cell Carcinoma	10-15%	Strong	Peripheral	Anaplastic, undifferentiated	Early, distant	53% early stage, 5% advanced stage

US Mortality Files, National Center for Health Statistics, CDC

Canadian Task Force on Preventive Health (2016)
Screening with low-dose CT recommended for high-risk patients only:
- 55-74 yr
- ≥30 pack-yr smoking Hx
- Current smoker or quit within last 15 yr
- Annual screening low-dose CT up to 3 yr

Risk Factors

- cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers
- risk of lung cancer increases with number of cigarettes smoked per day (linear) and duration of smoking (exponential)
- other risk factors: cigar smoking, pipe smoking, second-hand smoke, asbestos without smoking (relative risk is 5), asbestos with smoking (relative risk is 92), metals (e.g. chromium, arsenic, nickel), radon gas, ionizing radiation, and genetics

Clinical Features

- may be due to primary lesion, metastasis, or paraneoplastic syndrome
- primary lesion
  - cough (75%): beware of chronic cough that changes in character
  - dyspnea (60%)
  - chest pain (45%)
  - hemoptysis (35%)
  - other pain (25%)
  - clubbing (21%)
  - constitutional symptoms: anorexia, weight loss, fever, and fatigue
- metastasis
  - lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing, post-obstructive pneumonia
  - pericardium: pericardial effusion, pericardial tamponade
  - esophageal compression: dysphagia
  - phrenic nerve: paralyzed diaphragm, dyspnea
  - recurrent laryngeal nerve: hoarseness
  - superior vena cava syndrome
    - obstruction of SVC causing neck and facial swelling
    - other symptoms: dyspnea, cough, hoarseness, tongue swelling, epistaxis, and hemoptysis
    - physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton's sign (facial flushing, cyanosis, and distension of neck veins upon raising both arms above head)
    - milder symptoms if obstruction is above the azygos vein
  - lung apex (Pancoast tumour): Horner's syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
  - rib and vertebrae: erosion, pain
  - distant metastasis to brain, bone, liver, and adrenals
- paraneoplastic syndromes
  - most often associated with SCLC

Malignant lung tumours are the most common cause of cancer mortality in both men and women worldwide

Endobronchial Ultrasound (EBUS)

Allows visualization of peri-bronchial structures and lung lesions

Allows for guided biopsies of lymph nodes and tumours

Used for diagnosis and staging

Table 10. Paraneoplastic Syndromes

System	Clinical Features	Associated Malignancy
Skeletal	Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)	Non-small cell lung cancer (NSCLC)
Dermatologic	Acanthosis nigricans Dermatomyositis	Lung cancer
Endocrine	Hypercalcemia (osteolysis or PTHrP) Hypophosphatemia Hypoglycemia Cushing's syndrome (ACTH) Carcinoid syndrome SIADH	SCC SCC Sarcoma Small cell lung cancer (SCLC) Bronchial carcinoid SCLC
Neuromyopathic	Lambert-Eaton syndrome Polymyositis Subacute cerebellar degeneration Spinocerebellar degeneration Peripheral neuropathy	SCLC
Vascular/Hematologic	Nonbacterial endocarditis Trousseau's syndrome (migratory thrombophlebitis) DIC	Lung cancer NSCLC
Renal	Nephrotic syndrome	Lung carcinoma

Investigations

- initial diagnosis
  - imaging: CXR, CT chest + abdomen, PET scan
  - biopsy: bronchoscopy, EBUS, CT-guided percutaneous needle biopsy
- staging workup
  - TNM staging system: T – primary tumour (size); N – regional lymph nodes; M – distant metastasis
  - blood work: electrolytes, LFTs, calcium, ALP
  - imaging: CXR, CT thorax and abdomen, PET scan, bone scan (-in confirmed stage 4 cancer), neuroimaging (MRI Brain)
  - invasive: bronchoscopy (EBUS), mediastinoscopy, VATS

Table 11. SCLC vs. NSCLC

	Stage	Definition	Treatment	Median Survival
SCLC	Limited stage	Confined to single radiation port (one hemithorax and regional lymph nodes)	Radiation ± chemotherapy ± prophylactic to brain	1-2 yr (12 wk without treatment)
	Extensive stage	Extension beyond a single radiation port	Chemotherapy	6 mo (5 wk without treatment)
	Stage	**TNM**	**Treatment**	**5 Yr Survival (%)***
NSCLC	0	TisN0M0	1st line is complete surgical resection (VATS or open thoracotomy) with possible postoperative adjuvant chemotherapy with stage IB and stage II; radiotherapy for non-surgical candidates	
	IA1	T1aN0M0		90-92
	IA2	T1bN0M0		83-85
	IA3	T1cN0M0		77-80
	IB	T2aN0M0		68-73
	IIA	T2bN0M0		60-65
	IIB	T3N0M0 or T1N1M0 or T2N1M0		53-56
	IIIA	T4N0M0 or T4N1M0 or T3M1N0 or T1N2M0 or T2N2M0	Combined modality approach (chemo ± radiation, and sometimes surgical resection)	36-41
	IIIB	T3N2M0 or T4M2N0 or T1N3M0 or T2N3M0		24-26
	IIC	T3N3M0 or T4N3M0		12-13
	IVA	T1-4N0-3M1a-1b	Systemic therapy or molecularly targeted therapy or symptom-based palliative management (radiation); isolated metastasis may be resected	10
	IVB	T1-4N0-3M1c		0

* Depends on clinical vs. pathologic stage Refer to AJCC Cancer Staging Manual, 8th ed. 2017 for complete TNM classification

Treatment

- options include surgery, radiotherapy, ablation, chemotherapy, and palliative care for end-stage disease
- surgery not usually performed for SCLC since it is generally non-curable
- contraindications for surgery
  - spread to contralateral mediastinal lymph nodes or distant sites
    - patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
  - poor pulmonary status (e.g. unable to tolerate resection of lung)
    - postoperative estimated FEV $_1$and DLCO must be at least 40% of predicted to tolerate surgery
- chemotherapy (used in combination with other treatments)
  - common agents: cisplatin-vinorelbine (standard of care), etoposide, ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  - pembrolizumab, a PD-1 monoclonal antibody is used in those with tumour PD-L1 levels >50%; for those with PD-L1 levels <50%, combination of doublet chemotherapy and pembrolizumab is initiated

2/3 of primary lung cancer is found in the upper lung; 2/3 of metastases occur in the lower lung (hematogenous spread secondary to increased blood flow to the base of the lung)

Prevention
Smoking cessation
Avoidance of exposures
Early detection

Terminology
- "Nodule" <3 cm
- "Mass" >3 cm

Mutations in endothelial growth factor receptor are more common in non-smoking patients with adenocarcinoma

Corona Radiata Sign on Chest CT

Fine striations that extend linearly from a nodule in a spiculated fashion

Highly associated with malignancy

Carcinoids

Early onset (40-60 yr)

Most are central and can produce symptoms and signs of bronchial obstruction

Hemoptysis is present in ~50% of cases

Assuming adequate pulmonary function, surgical resection (i.e. segmentectomy, wedge resections, and lobectomy) is the preferred treatment approach

- targeted therapies such as EGFR tyrosine kinase inhibitors and ALK tyrosine kinase inhibitors are used if tumour tests positive for these mutations
- complications
  - acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
  - chronic: neurologic damage, leukemia, additional primary neoplasms

Pleura, Lung, and Mediastinum

- see Respirology, R23

Hamartomas

10% of benign lung lesions

Composed of tissues normally present in lung (fat, epithelium, fibrous tissue, and cartilage), but they exhibit disorganized growth

Peak incidence is age 60, more common in men

Usually peripheral and clinically silent

CXR shows clustered "popcorn" pattern of calcification (pathognomonic for hamartoma)

Peripheral small hamartomas can generally be observed with occasional follow-up to monitor growth; symptomatic endobronchial hamartomas are removed via rigid transbronchial resection

Complicated Parapneumonic Effusion

Definition
- persistent bacteria in the pleural space but fluid is non-purulent
- neutrophils, pleural fluid acidosis (pH<7.20), low glucose (<40 mg/dL)
- often no bacteria grown since rapidly cleared from pleural space

Clinical Features
- fever, pleuritic chest pain, dyspnea, and sputum production

Treatment
- antibiotics depending on Gram stain and culture
- chest tube drainage

Empyema

Definition
- bacteria in pleural space or an effusion with organisms seen on a Gram stain or culture (e.g. pleural fluid is grossly purulent in advanced stage empyema)
- positive culture is not required for diagnosis

Etiology
- contiguous spread from lung infection (most commonly anaerobes) or infection through chest wall (e.g. trauma, surgery)

Clinical Features
- fever, pleuritic chest pain, dyspnea, and sputum production

Investigations
- CT chest
- thoracentesis
  - PMNs (lymphocytes in TB) ± visible organisms on Gram stain

Treatment
- antibiotic therapy for at least 4-6 wk (rarely effective alone)
- complete pleural drainage with chest tube
- if loculated, more difficult to drain – may require surgical drainage with VATS, or fibrinolysis (surgical or tPA/DNAse) to allow lung re-expansion (decortication)

Pneumothorax

Definition
- presence of air in the pleural space
- can be classified as:
  - primary or secondary
  - open or closed
  - simple or tension or occult (only visible on CT scan)

Pathophysiology
- entry of air into pleural space raises intrapleural pressure causing partial or complete lung deflation

Etiology
- traumatic: penetrating or non-penetrating chest injuries
- iatrogenic: central venous catheter, thoracentesis, mechanical ventilation with barotrauma, surgery

- spontaneous: no history of trauma or other underlying cause
  - primary (no underlying lung disease)
    - spontaneous rupture of apical subpleural bleb (pockets of air) of lung into pleural space
    - smoker, male, family history, Marfan's syndrome
  - secondary (underlying lung disease)
    - rupture of subpleural bleb in the pleural space which can migrate along bronchioalveolar bronchoalveolar sheath to the mediastinum then to the intrapleural space
    - necrosis of lung tissue adjacent to pleural surface
    - pneumonia, abscess, PCP, lung cancer, COPD, CF, TB, lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), lung metastasis (e.g. sarcoma)

Clinical Features
- can be asymptomatic
- acute-onset pleuritic chest pain, dyspnea
- tachypnea, tachycardia
- tracheal deviation (contralateral deviation in tension pneumothorax)
- shock (in tension pneumothorax)
- ipsilateral diminished chest expansion
- decreased tactile/vocal fremitus
- hyperresonance
- ipsilateral diminished breath sounds

Investigations
- CXR
  - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  - large: decreased density and decreased volume of lung on side of pneumothorax
  - see Medical Imaging, MI4 and MI9

Tube thoracostomy can be completed under U/S guidance

Treatment
- primary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + O_2
  - symptomatic or large (>3 cm): aspiration or chest tube
  - unstable/tension pneumothorax: needle decompression then chest tube, VATS bullectomy, and pleurodesis if unsuccessful (25-50%)
- secondary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + O_2
  - symptomatic, large, or unstable: chest tube and VATS pleurodesis with or without bullectomy if unsuccessful

Tube Thoracostomy

Indications
- to drain abnormal air or fluid collections in the pleural space
  - hemothorax, pleural effusion, chylothorax, and empyema
  - pneumothorax, if:
    - large or progressive
    - patient is on mechanical ventilation
    - bronchopleural fistula
    - tension pneumothorax
- to treat symptomatic and/or recurrent pleural effusion
  - see Respirology, R24
  - for long-term drainage of malignant effusions use: 1. Tunneled pleural catheter; 2. Pleural drainage and Talc pleurodesis
  - via facilitation of pleurodesis - obliteration of the pleural space by instilling talc to cause fusion of parietal and visceral pleura

Complications
- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators
  - tubes may be placed outside the pleural cavity in the chest wall, or below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma, liver, spleen or vasculature
- risk of re-expansion pulmonary edema when large volumes of fluid are drawn off quickly (>1.0-1.5 L)

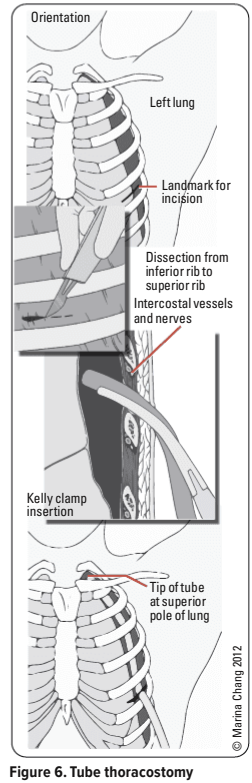

Orientation
Left lung
Landmark for incision
Dissection from inferior rib to superior rib
Intercostal vessels and nerves
Kelly clamp insertion
Tip of tube at superior pole of lung
© Marina Chang 2012

Figure 6. Tube thoracostomy

Lung Transplantation

Conditions Leading to Transplantation
- obstructive: chronic acquired lung disease (e.g. COPD), CF, and emphysema due to α-1 antitrypsin deficiency
- restrictive interstitial lung disease: IPF, hypersensitivity pneumonitis
- vascular: idiopathic pulmonary arterial HTN (IPAH), secondary pulmonary HTN, and Eisenmenger's syndrome
- other: sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis

Clinical Indications
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and have risk of death >50% over the next 2 yr

Criteria for Transplantation
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

Absolute Contraindications
- uncontrolled or untreatable pulmonary or extrapulmonary infection
- active TB infection
- malignancy in the last 2 yr
- dysfunction of vital organs including glomerular filtration rate of <40 mL/min/1.73 m^3, stroke within 30 d, acute liver failure or cirrhosis, acute coronary syndrome within 30 d or heart disease not amenable to revascularization, and untreatable hematologic disorders
- active cigarette smoking
- BMI ≥35 kg/m^2
- unresolved psychosocial problems or non-adherence to medical therapy
- smoking
- absence of social support system

Relative Contraindications
- ages >70 yr and low physiologic reserve
- BMI 30-34.9 kg/m^2
- limited functional status including severe malnutrition or osteoporosis
- HIV infection, HBV infection
- alcohol (required to stay within healthy drinking guidelines)

Postoperative Complications
- primary graft dysfunction
- airway anastomotic complications (bronchial necrosis and dehiscence, tracheobronchomalacia, stenosis)
- chronic lung allograft dysfunction (bronchiolitis obliterans syndrome and restrictive allograft syndrome)
- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, and mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disorders, colon, breast, Kaposi's sarcoma, and bladder)

Prognosis
- median survival for all adult recipients: 6.5 yr; bilateral transplant survival higher than single (7.6 vs. 4.7 yr, respectively)
- 1 yr survival: COPD > IPF > IPAH
- 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD, IPF

Chronic Obstructive Pulmonary Disease

- see Respirology, R9

Treatment
- indications for surgical management
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation

- contraindications
  - ages >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality (e.g. severe CAD or HF)
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - severe cachexia or obesity, chest wall deformity, or pulmonary HTN (PA systolic pressure >45 mmHg)
  - diffusing capacity of lung for carbon monoxide <20% of predicted, $PaCO_2$ >60 mmHg, PaO_2 <45 mmHg
- surgical procedures
  - lung volume reduction surgery: wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS (preferred)

Complications of Treatment
- arrhythmias, pneumonia (may require reintubation and mechanical ventilation), prolonged air leak from chest tube

Prognosis
- worse early mortality but better exercise capacity and quality of life with LVRS

Mediastinal Masses

Definition
- mediastinum: bound by the thoracic inlet, diaphragm, sternum, vertebral bodies, and the pleura
- can be broken down into 3 compartments: anterior, middle, and posterior

Etiology and Pathophysiology
- diagnosis is aided by location and patient's age
- anterior compartment: more likely to be malignant
  - "Four Ts" (see sidebar), lymphadenopathy, lipoma, pericardial cyst, goitre, and ascending aortic aneurysm thymic tumours/cysts
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumour, lymphadenopathy, aortic aneurysm
- posterior compartment
  - neurogenic tumours, meningocele, enteric cysts, lymphadenopathy, diaphragmatic hernias, esophageal tumours, aortic aneurysm

Clinical Features
- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner's syndrome (see sidebar), facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes (e.g. myasthenia gravis (thymomas))

Investigations
- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumours
- echocardiogram: best for assessment of structures in close proximity to the heart and pericardium
- radionuclide scanning: ^{131}I (for thyroid), gallium (for lymphoma), PET/CT
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP, β-hCG, LDH
- biopsy (mediastinoscopy, bronchoscopy, and EBUS, percutaneous needle aspiration)

Management
- excision – symptomatic benign mass that is enlarging or a mass with concerns for malignancy
- resect bronchogenic cysts and localized neurogenic tumours via VATS or open surgery
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
- no biopsy if AFP, β-hCG, LDH elevated – pathognomonic for germ cell tumour

Differential of an Anterior Compartment Mass

4 Ts
Thymoma
Thyroid enlargement (goitre)
Teratoma
Tumours (lymphoma, parathyroid, esophageal, angiomatous)

Mediastinal Components
Anterior: sternum to pericardium and great vessels. Includes: thymus, extra-pericardial aorta and branches, great veins, lymphatic tissues
Middle: pericardium (anteriorly), posterior pericardial reflection, diaphragm, thoracic inlet. Includes: heart, intrapericardial great vessels, trachea
Posterior: posterior pericardial reflection, posterior border of vertebral bodies, first rib to the diaphragm. Includes: esophagus, vagus nerve, thoracic duct, sympathetic chain, azygous venous system

Masaoka Staging System
Stage I: completely encapsulated
Stage II: invasion beyond capsule
Stage III: into another organ
Stage IVa: pleural/pericardial mets
Stage IVb: hematogenous/lymphatic mets

Thymoma

Definition
- rare neoplasms in thymus, located in anterior mediastinum

Epidemiology
- patients between 40 and 60 yr
- M=F
- no known risk factors, strong association with myasthenia gravis and other paraneoplastic syndromes

Clinical Features
- frequently asymptomatic: incidental finding on imaging
- symptoms related to tumour size and location (chest pain, SOB, cough, and phrenic nerve palsy)
- DDx includes intrathoracic goitre, lymphoma, and other anterior mediastinal tumours (see *Mediastinal Masses, GS20*)

Investigations
- CT chest (and/or MRI): assess resectability
- germ cell tumour markers (β-hCG, AFP, LDH), thyroid function, acetylcholinesterase antibodies (to rule out myasthenia gravis), and PFTs
- Masaoka staging system widely used

Treatment
- for patients with resectable disease
  - surgical resection of the thymoma and the thymus via median sternotomy or VATS depending on the size
  - ± postoperative radiation based on Masaoka staging
    - radiation considered for stage II/III disease
- for potentially unresectable disease (i.e. invasion into heart and great vessels) or non-surgical patients
  - definitive or palliative chemo and radiation therapy
- re-evaluation if debulking procedure feasible in situations where preoperative chemo- and radiation therapy is offered
- common chemotherapy regimens include: 1) cyclophosphamide, doxorubicin, and cisplatin, or 2) cisplatin and etoposide

Prognosis
- depends upon stage of disease and resectability
- generally slow-growing tumours and have good prognosis

Esophageal Carcinoma

Epidemiology
- M:F=3:1
- onset 50-60 yr
- upper (20-33%), middle (33%), and lower (33-50%)
- main types
  - most common worldwide: SCC in upper 2/3 of esophagus
  - most common in Western countries: adenocarcinoma in lower 1/3 of esophagus

Risk Factors
- SCC
  - underlying esophageal disease such as strictures, diverticula, and achalasia
  - smoking, alcohol, and hot liquids
  - more common in Black and Asian populations
- adenocarcinoma
  - Barrett's esophagus (most important), smoking, obesity (increased reflux), and GERD
  - more common in White populations

Clinical Features
- progressive dysphagia (mechanical): first solids then liquids, then saliva
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis and anemia
- direct, hematogenous, or lymphatic spread
  - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac, and mediastinal nodes

Investigations and Staging
- barium swallow: shows narrowing – suggestive but not diagnostic
- endoscopic biopsy to assess location, resectability, and confirm diagnosis
- both SCC and adenocarcinoma use TNM staging system but have separate stage groupings according to histology
- endoscopic U/S (EUS)
  - visualize local disease
  - regional nodal involvement (number of nodes may be more important than location)
- bronchoscopy and laryngoscopy
  - rule out airway invasion in tumours of the upper and middle esophagus
- full metastatic workup (CXR, bone scan, CT head, CT chest/abdomen/pelvis, and LFTs, etc.)
- PET scan more sensitive than CT in detecting metastatic disease

Treatment
- if early stage (non-transmural and without evidence of nodal disease)
  - endoscopic mucosal resection can be considered for early mucosal cancer or high-grade dysplasia
  - esophagectomy (transthoracic or trans-hiatal approach) and lymphadenectomy
    - anastomosis in chest or neck
    - stomach is used for reconstruction; colon is rarely used
- if locally advanced (locally invasive disease or nodal disease on CT or EUS)
  - multimodal therapy
    - concurrent external beam radiation and chemotherapy (cisplatin and fluorouracil)
    - possibility of curative esophagectomy after chemoradiation if unable to tolerate multimodal therapy or if highly advanced disease, consider radiotherapy, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if present with distant metastatic disease, treat with systemic therapy and treat symptoms (esophageal stent or radiation)

Prognosis
- TNM status - usually poor because presentation is usually at advanced stage

OTHER DISORDERS
- esophageal motor disorders (see Gastroenterology, G8)
- esophageal varices (see Gastroenterology, G9)
- Mallory-Weiss tear (see Gastroenterology, G30)

Esophageal Perforation

Etiology
- iatrogenic (most common)
  - endoscopic, dilatation, biopsy, intubation, operative, and NG tube placement (rare)
- barogenic
  - trauma
  - repeated, forceful vomiting (Boerhaave's syndrome)
  - other: convulsions, defecation, or labour (rare)
- ingestion injury
  - foreign body or corrosive substance
- carcinoma
- penetrating trauma

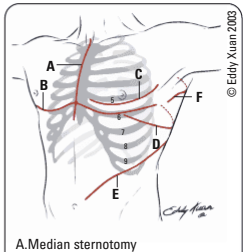
Clinical Features
- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, and respiratory compromise
- subcutaneous emphysema, pneumothorax, pleural effusion, voice changes, and hematemesis

Investigations
- CXR: subcutaneous emphysema, pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air, and widened mediastinum
- CT chest with oral and IV contrast: pneumomediastinum, pleural effusion, pneumothorax, contrast in the chest, and subcutaneous emphysema
- contrast esophagram
  - Gastrografin® (water-soluble contrast) upper GI study is the first choice
  - if negative, followed by dilute barium upper GI study: contrast extravasation

Treatment
- supportive if rupture is contained (see sidebar Cameron's Criteria)
- NPO, antibiotics, IV fluids, percutaneous drainage of mediastinal collections/abscess if needed, enteral/parenteral feed, and repeat imaging
- surgical (preferred treatment in progressively deteriorating or toxic patient)
  - <24 h from perforation
    - primary closure of a healthy esophagus with buttressed intercostal muscle flap or resection of diseased esophagus
  - >24 h from perforation, non-viable esophagus, or morbidly toxic patient
    - diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, and gastrostomy/jejunostomy for decompression/feeding)

Complications
- sepsis, abscess, fistula, empyema, mediastinitis, and death
- postoperative esophageal leak
- mortality 10-50% depending on timing of diagnosis, or etiology of the perforation, and underlying health and age of the patient

Cameron's Criteria for Conservative Management of Esophageal Perforation
- Perforation contained in mediastinum
- Contrast drains back into esophagus
- No signs of sepsis
- Minimal symptoms



A. Median sternotomy
B. Transverse thoracotomy (clam shell)
C. Anterolateral thoracotomy
D. Lateral thoracotomy
E. Thoracoabdominal thoracotomy
F. Posterolateral thoracotomy

Figure 7. Typical thoracic surgery incisions

Boerhaave's syndrome: transmural esophageal perforation
Mallory-Weiss tear: non-transmural esophageal tear (partial thickness tear)
Both are associated with forceful emesis

Standard of Care in 2019
1. Pre and postoperative FLOT chemotherapy for gastric and GE junction adenocarcinoma (docetaxel, oxaliplatin, and fluorouracil/leucovorin)
2. Neoadjuvant CROSS chemoradiotherapy for esophageal cancer with squamous histology or mid-body adenocarcinoma (carboplatin and paclitaxel plus radiotherapy)

6Ss of SCC
Smoking
Spirits (alcohol)
Seeds (betel nut)
Scalding (hot liquid)
Strictures
Sack (diverticula)

Hiatus Hernia

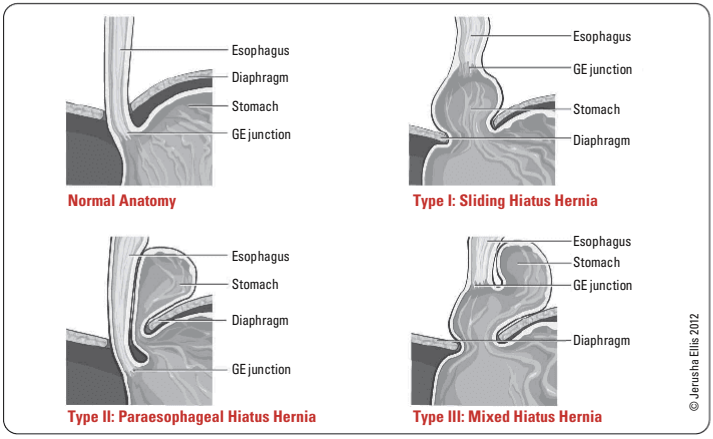


Figure 8. Types of hiatus hernia: Type I: Sliding (GE junction above the level of the diaphragm) Type II: Paraesophageal (GE junction below the diaphragm, fundus rolls past it) Type III: Mixed and Type IV: Massive (not shown) (containing another intra-abdominal organ: bowel/spleen/etc.)

SLIDING HIATUS HERNIA (TYPE I)

- reducible and/or limited herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

Risk Factors

- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, and heavy lifting)
- smoking

Clinical Features

- majority are asymptomatic
- symptoms in decreasing frequency are heartburn, regurgitation, eructation, sour taste, and cough

Complications

- complications are due to acid reflux when clinically significant and include these three categories:
  - esophagitis (dysphagia and heartburn)
  - consequences of esophagitis (peptic stricture, Barrett's esophagus, and esophageal carcinoma)
  - extra-esophageal complications (aspiration pneumonitis/pneumonia, bronchospasm, cough, and laryngitis)

Investigations

- barium study
- CXR or CT scan
- 24 h esophageal pH monitoring to quantify reflux and esophageal manometry (technique for measuring LES pressure)
- endoscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett's esophagus, and cancer

Treatment

- lifestyle modification
  - smoking cessation, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint, chocolate, and fatty foods
- medical
  - PPI, antacid, H2-antagonist, prokinetic agent
- surgical (<15% of cases)
  - consider if: volume regurgitation, patient unwilling or unable to stay on PPI indefinitely, suboptimal medical therapy, complications of GERD such as pharyngitis, esophageal stricture, recurrent nocturnal aspiration, Barrett's esophagus, patient preference
  - laparoscopic hiatus hernia repair and fundoplication
    - fundus of stomach is wrapped around the gastroesophageal junction and sutured in place

- operative principles are reduction of hernia, removal of hernia sac, fundoplication, and partial closure of hiatus
- 360 degree wrap: Nissen Fundoplication (most commonly performed). Dor, and Toupet are partial fundoplications
- expect transient postoperative clinical changes: dysphagia, bloating, excessive gas
- long-term complications may include post-prandial diarrhea and hernia recurrence in minority of patients
- dysphagia and gas bloat may be less with partial fundoplications (Toupet/Dor), however accompanied with higher risk of mild reflux symptoms
- 90% success rate for alleviating GERD

WebSurg
https://websurg.com/en/
WebSurg is an excellent resource which allows trainees to learn many different surgical techniques via videos and lectures. This resource primarily focuses on laparoscopic surgeries

PARAESOPHAGEAL HIATUS HERNIA (TYPE II)
- least common esophageal hernia (<10%)
- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction

Clinical Features
- usually asymptomatic due to normal GE junction
- dysphagia (most common), chest pain, and pressure sensation in lower chest

Complications
- hemorrhage, incarceration, strangulation (gastric volvulus), obstruction, gastric stasis ulcer (Cameron's lesion – causes Fe-deficiency anemia)

Elective laparoscopic procedures for paraesophageal hiatal hernia repair are associated with relatively low mortality. However, this value increases greatly with emergency repairs (7.5% vs. 0.5%)

MIXED HIATUS HERNIA (TYPE III)
- most common indication for surgical repair
- second most common type of hernia – combination of types I and II
- includes giant hernias or intrathoracic stomach
- rare incidence of gastric volvulus (Borschadt's Triad: chest pain, retching, inability to pass NG tube)
- may present with long-standing Fe-deficiency anemia of unknown etiology

Clinical Features
- symptoms may include reflux or heartburn
- most common symptoms: abnormal postprandial fullness after normal-sized meal, chest pain or retrosternal discomfort (gastric angina), and bloating
- can present with gastric outlet obstruction or gastric necrosis secondary to strangulation in the setting of gastric volvulus

Treatment
- surgery to address symptoms or treat/prevent complications
- reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
- may consider suturing stomach to anterior abdominal wall (gastropexy) to reduce the risk of gastric reherniation
- in very elderly patients at high surgical risk consider reduction of hernia and PEG (percutaneous endoscopic gastrostomy) insertion to anchor the stomach in the abdomen

TYPE IV HERNIA
- herniation of stomach and other abdominal organs into thorax: colon, spleen, pancreas, and small bowel
- similar presentation as type III hernia and may include intermittent large bowel symptoms (pain, hematochezia, constipation, etc.) if it is herniated

Achalasia

- esophageal smooth muscle motility disorder which occurs because the lower esophageal sphincter fails to relax
- esophagus does not have peristalsis
- in 50% of patients, the lower esophageal tone is hypertensive resulting in obstruction at the GE junction

Risk Factors
- spinal cord injury

Clinical Features
- dysphagia, initially solid than to liquids though a majority of patients will initially present with dysphagia to both solids and liquids
- regurgitation
- late symptoms include chest pain, nocturnal cough, and weight loss from difficulty eating

Investigations
- barium esophagram with a classic finding of smooth tapering of the lower esophagus to a "bird's beak" appearance
- upper endoscopy
- esophageal manometry will show incomplete lower esophageal sphincter relaxation in response to swallowing and sometimes a lack of peristalsis in the lower esophagus

Treatment
- non-surgical treatment:
  - pharmacologic: nitrates, calcium channel blockers, and phosphodiesterase-5 inhibitors to reduce LES pressure
  - endoscopic botulinum toxin injection
  - pneumatic dilation
- surgical treatment options:
  - laparoscopic Heller myotomy
  - peroral endoscopic myotomy

Complications
- esophageal perforation
- GERD
- bloating

Stomach and Duodenum

Peptic Ulcer Disease

GASTRIC ULCERS
- see Gastroenterology, G11

Indications for Surgery
- treat complications: bleeding (common indication for emergency management), perforation and obstruction (3x greater risk compared to duodenal ulcers)
- refractory to medical management–time period is unclear but generally after 8-12 wk of medical therapy
- suspicion of malignancy (even if biopsy is benign), especially if ulcer fails to heal after 12 wk of medical therapy
- surgery is becoming increasingly rare due to H. pylori eradication, medical treatment, endoscopic treatments (injection therapy with adrenaline, polidocanol, or fibrin glue) and coagulation therapy (heater probe or argon plasma)

Procedures
- ligation of bleeding vessels
- distal gastrectomy with ulcer excision: Billroth II, Roux-en-Y gastrojejunostomy, or Billroth I (rarely) reconstruction
- vagotomy and pyloroplasty only if acid hypersecretion (very rare)
- wedge resection if possible
- biopsy for suspicion of malignancy, followed by gastroscopy to minimize further bleeding and aid with healing

DUODENAL ULCERS
- see Gastroenterology, *Peptic Ulcer Disease, G11*
- most within 2 cm of pylorus (duodenal bulb)

Indications for Surgery
- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
- refractory to medical and endoscopic management

Procedures
- omental (Graham) patch: plication of perforated ulcer supported by overlying omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- treat with *H. pylori* eradication protocol postoperatively

Complications of Gastric Surgery
- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome

Table 12. Complications of Duodenal Ulceration

Complication	Clinical Features	Management
Perforated Ulcer (typically on anterior surface)	Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter) Acute abdomen: rigid, diffuse guarding Ileus Initial chemical peritonitis followed by bacterial peritonitis	Investigation CXR free air under diaphragm (70% of patients) Treatment Oversew ulcer (plication) and omental (Graham) patch most common treatment
Penetration to Nearby Organs	Elevated amylase/lipase if penetration into pancreas Elevated hepatic transaminases if penetration into liver (rare, but serious) Constant mid-epigastric pain burrowing into back, unrelated to meals	Management should follow the intensive measures for refractory ulcers
Hemorrhage (typically on posterior surface)	Gastroduodenal artery involvement	Resuscitation initially with crystalloids; blood transfusion if necessary Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope Consider interventional radiology: angiography with embolization/coiling Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty
Gastric Outlet Obstruction	Ulcer can lead to edema, fibrosis of pyloric channel, and neoplasm N/V (undigested food, non-bilious), dilated stomach, and crampy abdominal pain Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken) Auscultate gas and fluid movement in obstructed organ	NG tube decompression and correction of hypochloremic, hypokalemic metabolic alkalosis Medical management initially: high-dose PPI therapy Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty, or gastrojejunostomy

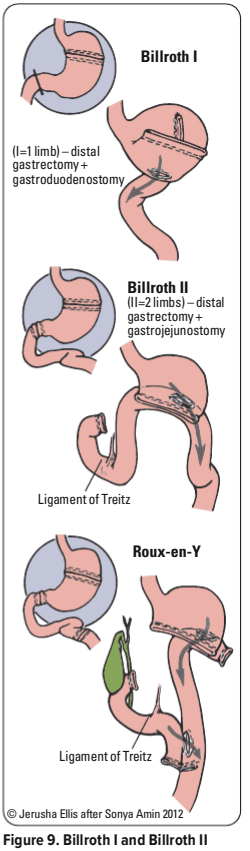

Billroth I
(I=1 limb) – distal gastrectomy + gastroduodenostomy
Billroth II
(II=2 limbs) – distal gastrectomy + gastrojejunostomy
Ligament of Treitz
Roux-en-Y
Ligament of Treitz
© Jerusha Ellis after Sonya Amin 2012

Figure 9. Billroth I and Billroth II with Roux-en-Y reconstruction (gastrojejunostomy)

Gastric Carcinoma

Epidemiology

- 5th most common cancer in the world
- M:F=3:2
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr
- incidence highest in Asian, Latin American, and Caribbean countries

Risk Factors

- compensatory epithelial cell proliferation via gastric atrophy from:
  - *H. pylori*, causing chronic atrophic gastritis
  - pernicious anemia associated with achlorhydria and chronic atrophic gastritis
  - previous partial gastrectomy (>10 yr post-gastrectomy)
- lifestyle and environmental factors:
  - salt and salt-preserved food (e.g. salted fish, cured meat, and salted vegetables)
  - obesity
  - cigarette smoking
  - EBV infection
  - abdominal radiation therapy
- host-related factors
  - blood type A – also associated with pernicious anemia
  - hereditary nonpolyposis colorectal cancer (HNPCC), hereditary diffuse gastric carcinoma (HDGC)
  - gastric adenomatous polyps
  - hypertrophic gastropathy
  - genetic syndromes: hereditary diffuse gastric cancer (e.g. E-cadherin (CDH1)) gene

Clinical Features

- clinical suspicion
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious, or late onset of symptoms
  - postprandial abdominal fullness, pseudoachalasia (in older patients), vague epigastric pain
  - anorexia or weight loss
  - eructation, N/V, dyspepsia, and dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, and iron-deficiency anemia
- metastasis
  - peritoneum, ovarian, liver, lung, and brain

Investigations

- OGD and biopsy; consider EUS to assess preoperative T-stage and N-stage
- CT chest/abdomen/pelvis (with gastric protocol)

Kissing Ulcer: combination of perforation and bleeding

Signs of Metastatic Gastric Carcinoma
Virchow's Node: left supraclavicular node
Blumer's Shelf: mass in pouch of Douglas
Krukenberg Tumour: metastases to ovary
Sister Mary Joseph Node: umbilical metastases
Irish's Node: left axillary nodes

Table 13. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2017, 8th edition)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	**NX**	Cannot be assessed	**M0**	No distant metastasis
T0	No evidence of primary tumour	**N0**	No regional node metastasis	**M1**	Distant metastasis
Tis	Carcinoma *in situ*	**N1**	Metastasis in 1-2 regional nodes		
T1a	Invasion into lamina propria or muscularis mucosae	**N2**	Metastasis in 3-6 regional nodes		
T1b	Invasion into submucosa	**N3a**	Metastasis in 7-15 regional nodes		
T2	Invasion into muscularis propria	**N3b**	Metastasis in ≥16 regional nodes		
T3	Penetration of subserosal connective tissue without tissue invasion of visceral peritoneum or adjacent structures				
T4a	Invasion into serosa				
T4b	Invasion into adjacent structures				

Treatment

- adenocarcinoma
  - proximal lesions
    - total gastrectomy and Roux-en-Y esophagojejunostomy
  - distal lesions
    - subtotal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes (D2 lymphadenectomy) with Roux-en-Y or Billroth II reconstruction
  - adjuvant therapies
    - perioperative chemotherapy or postoperative chemoradiotherapy in addition to surgery is standard of care in a curative intent strategy
  - palliation
    - limited gastric resection or endoscopic stenting to decrease bleeding and relieve obstruction, enables the patient to eat
    - radiation therapy
    - studies are showing larger role for palliative chemotherapy
- lymphoma
  - *H. pylori* eradication, chemotherapy ± radiation, and surgery in limited cases (perforation, bleeding, and obstruction)

Staging and 5 Yr Survival Rates for Gastric Cancer

Stage	TNM	5 Yr Survival
IA	T1N0M0	71%
IB	T2N0M0	57%
	T1N1M0	
IIA	T3N0M0	45%
	T2N1M0	
	T1T2M0	
IIB	T4aN0M0	33%
	T3N1M0	
	T2N2M0	
	T1N3M0	
IIIA	T4aN1M0	20%
	T3T2M0	
	T2N3M0	
IIIB	T4bN0M0	14%
	T4bN1M0	
	T4aN2M0	
	T3N3M0	
IIIC	T4bN2M0	9%
	T4bN3M0	
	T4aN3M0	
IV	TxNxM1	4%

Gastrointestinal Stromal Tumour

Epidemiology

- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- often discovered incidentally on CT, laparotomy, or endoscopy

Neoadjuvant Chemotherapy in Advanced Gastric and Esophago-Gastric Cancer. Meta-Analysis of Randomized Trials
Int J Surg 2018;51:120-127
Study: Meta-analysis evaluating the effects of neoadjuvant chemotherapy on advanced gastric cancer.
Results/Conclusions: Neoadjuvant chemotherapy and resection reduces overall mortality at 3 and 5 yr in advanced gastric cancer (RR=0.74; 0.82 respectively). Morbidity and perioperative mortality rate are not influenced by NACT. Recurrence rate is reduced by NACT + surgery in EGC (RR=0.80).

Risk Factors

- Carney triad: gastric GISTs, extra-adrenal paraganglioma, and pulmonary chondroma
- type I neurofibromatosis
- Carney-Stratakis syndrome

Clinical Features

- most commonly in stomach (40-60%) and jejunum (25-30%)
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- sometimes asymptomatic (13-18%)
- nonspecific symptoms (8-17%): bloating, early satiety, abdominal pain/discomfort
- overt or occult GI bleeding (50% of gastric GISTs)

Investigations

- contrast-enhanced CT is preferred imaging for screening and staging; MRI if IV contrast not feasible
- preoperative biopsy (EUS): useful for indeterminate lesions (not recommended if high index of suspicion for GIST)
- given that lesions are submucosal, mucosal biopsies are sometimes non-diagnostil

Treatment
- surgical resection if >2 cm; follow with serial endoscopy if <2 cm (gastric GIST) and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT required as GISTs rarely metastasize to lymph nodes
  - consider adjuvant treatment with imatinib (Gleevec®) if high-risk of relapse (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - palliative intent chemotherapy with imatinib
  - metastasectomy may be considered for liver limited disease

Prognosis
- risk of metastatic potential depends on
  - tumour size (worse if >10 cm)
  - mitotic activity (worse if >5 mitotic figures/50 HPF)
  - degree of nuclear pleomorphism
  - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- frequently metastasize to the liver and omentum; nodal and lung metastases rare

Extent of Lymph Node Dissection for Adenocarcinoma of the Stomach
Cochrane DB Syst Rev 2015;12:CD001964
Study: Systematic review and meta-analysis on the evidence that existed regarding the impact of the three main types of progressively more extended lymph node dissection (that is, D1, D2 and D3 lymphadenectomy) on the clinical outcome of patients with primary resectable carcinoma of the stomach.
Results/Conclusions: Data suggested no significant difference in overall survival between D2 and D3 type dissection. There was no significant difference in overall survival between D1 and D2 type node dissection. In contrast, D2 lymphadenectomy was associated with a significantly better disease specific survival compared to D1 lymphadenectomy but was also associated with a higher postoperative mortality rate.

Bariatric Surgery

- weight reduction surgery for morbid obesity
- indications: BMI ≥35 without illness or BMI ≥30 with 1+ serious comorbidity (e.g. DM, CAD, sleep apnea, GERD, or severe joint disease)
  - Asian patients: growing evidence to lower BMI criteria by 2.5 (i.e. BMI ≥37.5 or BMI ≥35.5) due to higher prevalence of truncal obesity
- consult with a multidisciplinary bariatric team: nutrition, psychological deterrents, life modifications, lifelong surveillance, reliable bariatric program (details realistic outcomes) to optimize success post-operation

Surgery for Weight Loss in Adults
Cochrane DB Syst Rev 2014;8:CD003641
Study: Update of a 2003 Cochrane review assessing the effects of bariatric surgery and control of comorbidities.
Conclusions: Surgery resulted in decreased BMI one to two years postoperative. 3 RCTs found that laparoscopic Roux-en-Y gastric bypass achieved significantly greater weight loss and BMI reduction up to 5 yr after surgery compared with laparoscopic adjustable gastric banding (mean difference -5.2 kg/m^2; 95% CI -6.4 to -4.0). More patients experienced remission of diabetes with lap R-en-Y, however, different definitions were used. Risks of surgery include leaks, hernias, infection, pulmonary embolism, cholecystitis, and postoperative mortality.

Surgical Options
- combination malabsorptive and restrictive
  - laparoscopic Roux-en-Y gastric bypass (most common, most effective; higher complication rates)
    - small gastric pouch (restrictive), from distal stomach, anastomosed with Roux limb of small bowel (malabsorptive); connect to biliopancreatic limb to maintain digestive enzymes and bile
    - complications: gastric remnant distention, stomal stenosis, marginal ulcers, cholelithiasis, ventral incisional hernia, short bowel syndrome, dumping syndrome, metabolic perturbations, gastrogastric fistula
  - restrictive laparoscopic sleeve gastrectomy
    - creation of tubular stomach via removal of majority of greater curvature
    - complications: bleeding from gastric or short gastric vessels from dissection of greater curve, stenosis at the gastroesophageal junction, gastric leaks
- malabsorptive
  - biliopancreatic diversion with duodenal switch (performed as a rescue operation after traditional Roux-en-y)
    - anastomosis of stomach to distal ileum, anastomosis of biliopancreatic limb to terminal Ileum
    - complications: protein calorie malnutrition, anemia, metabolic bone disease, fat-soluble vitamin deficiency

Complications of Gastric Surgery
- most resolve within 1 yr
- important to note that morbidly obese patients usually do not present with the symptoms and signs shown below; often times, the only presenting sign is tachycardia

Alkaline Reflux Gastritis
- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment
  - medical: H2-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  - surgical: conversion of Billroth I or II to Roux-en-Y

Afferent Loop Syndrome
- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features
  - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
- treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Dumping Syndrome
- early: 15-30 min postprandial
  - etiology
    - rapid emptying of hyperosmotic chyme leads to jejunal distention, stimulating release of vasoactive hormones
  - clinical features
    - postprandial epigastric cramping, bloating, emesis, nausea, and vasomotor symptoms (dizziness, palpitations, tachycardia, diaphoresis)
  - treatment
    - frequent small meals high in fibre and protein, low in carbohydrates; avoidance of liquids with meals
    - last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late: 3 h postprandial
  - etiology: hypoglycemia following postprandial insulin peak
  - treatment: small snack 2 h after meals

Blind-Loop Syndrome
- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features
  - anemia/weakness, diarrhea, malnutrition, abdominal pain, and hypocalcemia
- treatment: broad-spectrum antibiotics and surgery (conversion to Billroth I)

Postvagotomy Diarrhea
- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine) and surgical (reversed interposition jejunal segment)

SMALL INTESTINE

Small Bowel Obstruction

Mechanical Small Bowel Obstruction

Pathophysiology
- obstruction → gas and fluid (swallowed or GI secretions) accumulate proximal to site of obstruction and distal decompression → intestinal activity increases to overcome obstruction → colicky pain and diarrhea (initially)

Etiology

Table 14. Common Causes of SBO

Intraluminal Foreign Body	Intramural	Extramural (>85% of causes)
Intussusception Gallstones (gallstone ileus) Bezoars Foreign body	Crohn's Radiation stricture Neoplasm (adenocarcinoma, carcinoid, lymphoma, sarcoma)	Adhesions from previous surgeries (75% SBO) Incarcerated hernia Peritoneal carcinomatosis

- AAST grading system for severity (Grade - "Operative Criteria")
  - partial SBO - minimal intestinal distension with no evidence of obstruction
  - complete SBO with viable bowel - intestinal distension with transition point: no bowel compromise
  - complete SBO with compromised but viable bowel - intestinal distension with impending bowel compromise
  - complete SBO with nonviable bowel or perforation and localized spillage - intestinal distension with localized perforation or free fluid
  - small bowel perforation with diffuse peritoneal contamination - intestinal distension with perforation, free fluid, and diffuse peritonitis
- closed-loop obstruction is when a segment is obstructed in two separate locations, creating a segment with no proximal or distal outlet and can rapidly progress to complications and require immediate abdominal exploration

Risk Factors
- prior abdominal or pelvic surgery (adhesions)
- abdominal wall or groin hernia
- personal history or increased risk of malignancy
- prior radiation

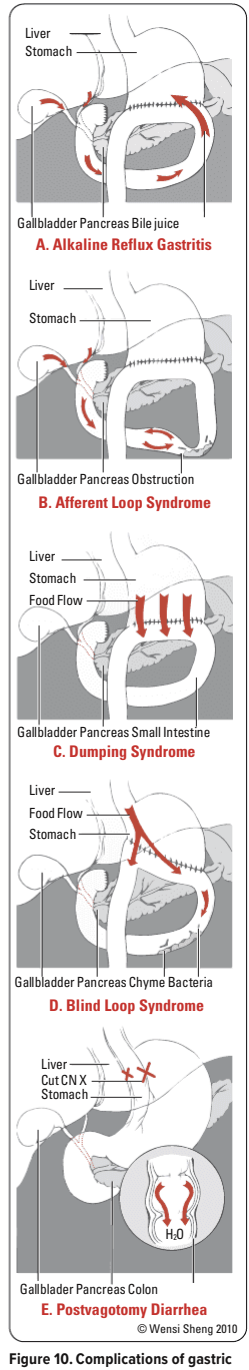


Figure 10. Complications of gastric surgery

- IBD
- history of foreign body ingestion

Clinical Features
- symptoms: colicky periumbilical abdominal pain, N/V, obstipation, delayed passage/inability to pass flatus, inability to tolerate an oral diet
  - more feculent vomitus suggests more established obstruction because of bacterial overgrowth
  - passage of gas and/or stool that continues 6-12 h after onset of symptoms suggests partial rather than complete obstruction
  - inability to pass flatus is the most useful indicator
- signs: abdominal distention (most prominent if obstruction at distal ileum), hyperactive proceeding to minimal bowel sounds, bloating, hypovolemia, hyperresonance with percussion
- strangulated obstruction: abdominal pain disproportionate to physical exam findings suggest intestinal ischemia
  - may have tachycardia, localized abdominal tenderness, fever, marked leukocytosis, and lactic acidosis

Investigations
- approach
  1. distinguish mechanical obstruction from ileus
  2. determine likely and easily reversible etiology of obstruction
  3. differentiate complicated (e.g. strangulated) obstruction
- imaging
  - usually if you suspect a bowel obstruction, a CT scan is the first line. Further, once CT scan confirms a bowel obstruction,, we perform 6 and 12 hour X-rays after giving water soluble contrast which is diagnostic for obstruction and often therapeutic
  - CT with IV contrast: discrete transition zone/point with proximal bowel dilation, distal bowel decompression, and intraluminal contrast does not pass the transition zone
    - most importantly to rule out ischemic bowel/strangulation: pneumatosis intestinalis (free air in bowel wall) and thickened bowel wall, air in portal vein, free intraperitoneal fluid, and differential wall enhancements (poor uptake of IV contrast into the wall of the affected bowel)
  - other (less common)
    - upper GI series/small bowel series (if no cause apparent, i.e. no hernias, and no previous surgeries)
    - serial CTs with oral contrast
    - may consider U/S or MRI in pregnant patients
- laboratory
  - may be normal early in disease course
  - CBC, electrolytes, BUN, creatinine, lactate
  - creatinine and hematocrit to assess degree of dehydration
  - may have fluid and electrolyte abnormalities with metabolic alkalosis due to frequent emesis
  - if strangulation: leukocytosis with left shift, elevated lactate (late signs)

Treatment
- IV isotonic fluid resuscitation and urine output monitoring with catheter
  - SBO related vomiting and decreased PO intake leads to volume depletion
- NG tube in the stomach for gastric decompression; decrease nausea, distention, and risk of aspiration from vomiting
- NPO
- if partial SBO/Crohn's/Carcinomatosis: conservative management with fluid resuscitation and NG tube decompression
  - 48 h of watchful waiting; if no improvement or develops complications, surgery
  - for Crohn's patients, consider GI consult for steroid management
- if no clinical features of ischemia: short course of conservative management with fluid resuscitation and NG tube decompression with frequent re-examination by surgical team
  - duration of observation varies from hours to a few days
  - if SBO fails to resolve, or if symptoms of ischemia develop, then surgery
- if high-risk for ischemia based on clinical symptoms: urgent surgery to prevent irreversible ischemia
  - early postoperative SBO: if bowel function does not return within 3-5 d after surgery; usually partial, extended conservative therapy (2-3 wk) with bowel rest, fluids, and TPN is appropriate
- immediate surgery if ischemia, necrosis, and perforation
  - clinical signs: fever, leukocytosis, tachycardia, worsening pain, metabolic and lactic acidosis, and tachypnea
  - radiologic signs: free air on radiographs or CT, closed-loop obstruction, abnormal course of a mesenteric vessel, and high-density free fluid

Prognosis
- related to etiology; mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%
- surgical intervention associated with a lower risk of recurrence

Prevention
- open surgery has four-fold increase in risk of SBO in 5 yr compared to laparoscopic surgery

Increased Risk of Perforation with Distention as seen on Abdomen Imaging
Small bowel ≥3 cm
Distal colon ≥6 cm
Proximal colon ≥9 cm
Cecum ≥12 cm

Important to know if chronic vs. acute. Chronic distention is more likely to be tolerated without perforation

Patients with NO Abdominal Surgery History ("Virgin Abdomen")
Presenting with a SBO should have surgery ASAP (EXCEPTION: malignant obstruction from history and imaging)

Patients with Abdominal Surgery History ("Non-virgin Abdomen")
Adhesional SBOs resolve spontaneously with NG tube decompression 70% of time

Top 3 Causes of SBO (in order)

ABC
Adhesions
Bulge (hernias)
Cancer (neoplasms)

Causes of SBO

SHAVING
Stricture
Hernia
Adhesions
Volvulus
Intussusception/IBD
Neoplasm
Gallstones

Paralytic Ileus

Pathogenesis
- temporary, reversible impairment of intestinal motility; most frequently caused by:
  - abdominal operations, infections and inflammation, medications (opiates, anesthetics, psychotropics), and electrolyte abnormalities
  - often seen for patients in the postoperative setting from intra-abdominal sepsis (perforated appendicitis, diverticulitis, etc.)
  - pathophysiology related to inhibitory splanchnic reflexes, inhibitory sympathetic activity, inflammatory stress response, peptides (VIP, substance P, Calcitonin gene-related peptide (CGRP))
- NOT the same as intestinal pseudo-obstruction
  - chronic pseudo-obstruction refers to specific disorders that affect the smooth muscle and myenteric plexus, leading to irreversible intestinal dysmotility

Clinical Features
- symptoms and signs of intestinal obstruction without mechanical obstruction
  - bowel sounds are diminished or absent (in contrast to initial hyperactive bowel sounds in SBO)
  - pain is often diffuse and less frequently has the colicky pattern present in mechanical obstruction
  - passing gas is the most useful indicator
- postoperative: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d

Investigations
- routine postoperative ileus: expected, no investigation needed
- if ileus persists or occurs without abdominal surgery
  - review patient medications (especially opiates)
  - measure serum electrolyte to monitor for electrolyte abnormalities (including extended electrolytes like Mg^{2+}, Ca^{2+}, PO_4^{3-})
  - creatinine and BUN
  - LFTs
  - CT scan to rule out abscess or peritoneal sepsis, or to exclude mechanical obstruction

Treatment
- address underlying cause
- most important initial treatment: NPO + fluid resuscitation
- for prolonged ileus: NG tube decompression, TPN, and pain management

Intestinal Ischemia

Etiology
- acute
  - arterio-occlusive mesenteric ischemia (AOMI)
    - thrombotic, embolic, and extrinsic compression (e.g. strangulating hernia)
  - non-occlusive mesenteric ischemia (NOMI)
    - mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  - mesenteric venous thrombosis (MVT)
    - consider hypercoagulable state (i.e. rule out malignancy) and DVT (prevents venous outflow)
- chronic: usually due to atherosclerotic disease – look for cardiovascular risk factors
- can lead to occlusion in vessels that supplies the small intestine and the large intestine

Pain "out of keeping with physical findings" is the hallmark of early intestinal ischemia

Clinical Features
- acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, and sepsis
- chronic: postprandial pain (from mesenteric angina), fear of eating, and weight loss
- common sites: SMA supplied territory, "watershed" areas of colon – splenic flexure, left colon, and sigmoid colon

Investigations
- laboratory: leukocytosis (non-specific) and lactic acidosis (late finding)
  - lactate used to observe progress
  - hypercoagulability workup if suspect venous thrombosis
- AXR: portal venous gas, intestinal pneumatosis, and free air if perforation
- contrast CT: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, and pneumatosis
- CT angiography is the gold standard for acute arterial ischemia

An acute abdomen + metabolic acidosis is bowel ischemia until proven otherwise

Treatment
- fluid resuscitation, correct metabolic acidosis, NPO, NG tube decompression of stomach, and prophylactic broad-spectrum antibiotics; avoid vasoconstrictors and digitalis
- exploratory laparotomy/laparoscopy to assess extent of viability ± segmental resection of necrotic intestine
  - if extent of bowel viability is uncertain, a second-look laparotomy 12-24 h later is mandatory
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, and percutaneous transluminal angioplasty ± stent

Tumours of Small Intestine

BENIGN TUMOURS

- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum and proximal jejunum
- polyps
  - adenomas
  - hamartomas
  - FAP (see *Familial Colon Cancer Syndromes, GS42*)
  - juvenile polyps
- other: leiomyomas, lipomas, and hemangiomas

Table 15. Malignant Tumours of the Small Intestine

	Adenocarcinoma	Carcinoid/GI NET-Neuroendocrine Tumour	Lymphoma	Metastatic
Epidemiology	Usually 50-70 yr M>F	Increased incidence 50-60 yr	Highest incidence in 70s M>F Usually non-Hodgkin's lymphoma	Most common site of GI metastases in patients with metastatic melanoma
Risk Factors	Crohn's, FAP, history of CRC, HNPCC		Crohn's, celiac disease, autoimmune disease, immunosuppression, radiation therapy, and nodular lymphoid hyperplasia	Melanoma, breast, lung, ovary, colon, and cervical cancer
Origin/Location	Usually in proximal small bowel, incidence decreases distally	Classified based on embryological origin (foregut, midgut, and hindgut) Originate from gut enterochromaffin cell Appendix 46%, distal ileum 28%, rectum 17%	Usually distal ileum Proximal jejunum in patients with celiac disease	Hematogenous spread from breast, lung, and kidney Direct extension from cervix, ovaries, and colon
Clinical Features	Early metastasis to lymph nodes 80% metastatic at time of operation Abdominal pain (common)	N/V, anemia, GI bleeding, jaundice, and weight loss (less common) Often slow-growing Usually asymptomatic, incidental finding Obstruction, bleeding, crampy abdominal pain, and intussusception Carcinoid syndrome (<10%) Hot flashes, hypotension, diarrhea, bronchoconstriction, and right heart failure Requires liver involvement: lesion secretes serotonin, kinins, and vasoactive peptides directly to systemic circulation (normally inactivated by liver)	Fatigue, weight loss, fever malabsorption, abdominal pain, anorexia, vomiting, constipation, and mass Rarely perforation, obstruction, bleeding, and intussusception	Obstruction and bleeding
Investigations	CT abdomen/pelvis Endoscopy	Most found incidentally at surgery for obstruction or appendectomy CT thorax/abdomen/pelvis Consider small bowel enteroclysis to look for primary Serum chromogranin A as a tumour marker Elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood Some nuclear medicine testing available but should be done by endocrine oncologist. Testing includes Galium DOTATATE PET scans and octreotide scans	CT abdomen/pelvis	CT abdomen/pelvis
Treatment	Surgical resection ± chemotherapy	Surgical resection ± chemotherapy Carcinoid syndrome treated with octreotide Metastatic risk 2% if size <1 cm, 90% if >2 cm	Low-grade: chemotherapy with cyclophosphamide High-grade: surgical resection, and radiation Palliative: somatostatin, doxorubicin	Palliation
Prognosis	5 yr survival 25% (if node positive)	5 yr survival 70%; 20% with liver metastases Based on the Ki67 index	5 yr survival 40%	Poor
Staging System	TNM	TNM	Ann Arbor	

Carcinoid Syndrome Symptoms

FDR
Flushing
Diarrhea
Right-sided heart failure

Indirect Inguinal Hernias: Rule of 5s

5% lifetime incidence in males
5x more common than direct inguinal hernias
5-10x more common in males than females
Generally occur by **5**th decade of life

Short Gut Syndrome

Definition
- reduced surface area (length) of small bowel causing insufficient intestinal absorption leading to diarrhea, malnutrition, and dehydration

Etiology
- due to surgical resection
  - large amount of bowel at once (acute mesenteric ischemia, trauma, malignancies)
  - cumulative resections (Crohn's disease)
- in infant and pediatric patients, the most common causes are necrotizing enterocolitis, abdominal wall defects, jejunal ileal atresia, and midgut volvulus

Prognostic Factors
- residual small bowel length, residual colon length (reabsorption of water and electrolytes and some reabsorption of nutrients), condition of the remnant small bowel (healthier bowel facilitate better reabsorption), presence of ileocecal valve (delay transition into colon leading to more reabsorption)
- resection of ileum is less tolerated than resection of jejunum (ileum reabsorbs bile salt and vitamin B_{12})

Therapy
- medical
  - IV fluids in acute management (initial 3-4 wk following resection) and TPN once stabilized to replenish lost fluid and electrolytes in diarrhea
  - histamine 2-receptor antagonist or PPI to prevent gastric acid secretion
  - antimotility agent to prolong transit time in the small intestine
  - consider octreotide to decrease GI secretion and cholestyramine for bile acid absorption
- surgical: non-transplant
  - to slow transit time: small bowel segmental reversal, intestinal valve construction, or electrical pacing of small bowel
  - to increase intestinal length:
    - LILT (longitudinal intestinal lengthening and tailoring) procedure
    - STEP (serial transverse enteroplasty procedure) in dilated small bowels
- surgical: small bowel transplant
  - indication: life-threatening complication from intestinal failure or long-term TPN, including liver failure, thrombosis of major central veins, recurrent catheter-related sepsis, and recurrent severe dehydration

Abdominal Hernia

• see *Hiatus Hernia, GS23*

Definition
- defect in abdominal wall causing abnormal protrusion of intra-abdominal contents

Epidemiology
- M:F=9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- frequency of occurrence: 50% indirect inguinal, 25% direct inguinal, 8-10% incisional (ventral), 5% femoral, and 3-8% umbilical
- most common surgical disease in males

Risk Factors
- activities which increase intra-abdominal pressure
  - obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, and heavy lifting
- congenital abnormality (e.g. patent processus vaginalis and indirect inguinal hernia)
- previous hernia repair, especially if complicated by wound infection
- loss of tissue strength and elasticity (e.g. hiatal hernia, aging, and repetitive stress)
- family history

Clinical Features
- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

Investigations
- physical examination usually sufficient
- U/S ± CT (CT required for obturator hernias, internal abdominal hernias, and Spigelian and/or femoral hernias in obese patients)

Inguinal Hernias

MD's don't LIe
MD: **M**edial to the inferior epigastric a. = **D**irect inguinal hernia
LI: Lateral to the inferior epigastric a. = **I**ndirect inguinal hernia
Inguinal Canal Walls = MALT x 2

2 M Roof	2 muscles (internal oblique, transversus abdominis)
2 A Ant. wall	2 aponeuroses (external and internal oblique)
2 L Floor	2 ligaments (inguinal and lacunar)
2 T Post. wall	2T (transversalis fascia, conjoint tendon)

Borders of Hesselbach's Triangle
- Lateral: inferior epigastric artery
- Inferior: inguinal ligament
- Medial: lateral margin of rectus sheath

Shouldice Technique vs. Other Open Techniques for Inguinal Hernia Repair
Cochrane DB Syst Rev 2012;4:CD001543
Purpose: To evaluate the efficacy and safety of the Shouldice technique compared to other non-laparoscopic techniques.
Results/Conclusions: 16 RCTs or quasi-randomized RCTs with 2566 hernias (1121 mesh; 1608 non-mesh). The recurrence rate with Shouldice was higher than mesh (OR 3.80, 95% CI 1.99-7.26) but lower than non-mesh (OR 0.62, 95% CI 0.45-0.85). There was no difference in chronic pain or complications. In conclusion, with respect to recurrence rates, Shouldice herniorrhaphy is the best non-mesh technique, although inferior to mesh. However, it is also more time consuming and results in slightly longer postoperative hospital stays.

Long-Term Results of a Randomized Controlled Trial of a Nonoperative Strategy (Watchful Waiting) for Men with Minimally Symptomatic Inguinal Hernias
Ann Surg 2013;258:508-514
Purpose: Ascertaining the long-term crossover (CO) rate in patients with asymptomatic or minimally symptomatic inguinal hernias undergoing watchful-waiting (WW) as their primary treatment modality.
Background: A 2006 RCT comparing WW with routine inguinal hernia repair, concluded that WW was an acceptable option in the management of male patients with minimal symptoms (JAMA 2006;295(3):285-292). This study analyzes the WW group after 7 yr of follow-up.
Conclusions: The estimated CO rate for the WW cohort was 68%, while men older than 65 had a rate of 79%. Therefore, while WW is a safe strategy, it is likely that symptoms will progress, and definitive surgical management will be indicated.

Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias
JAMA Surg 2013;148:1043-1048
See Landmark General and Thoracic Surgery Trials table for more information on outcomes of patients electively undergoing laparoscopic ventral hernia repair (LVHR) vs. open ventral hernia repair (OVHR)

Classification
- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  - requires emergency repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter's hernia: only part of bowel circumference (usually antimesenteric border) is incarcerated or strangulated so may not be obstructed
  - a strangulated Richter's hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation in the absence of obstructive symptoms
- sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)

Anatomical Types
- groin
  - indirect and direct inguinal, femoral
  - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre's (involving Meckel's), Amyand's (containing appendix), lumbar, obturator, peristomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

Complications
- incarceration
- strangulation
  - small, new hernias more likely to strangulate
  - femoral > indirect inguinal > direct inguinal
  - intense pain followed by tenderness
  - intestinal obstruction, gangrenous bowel, sepsis
  - surgical emergency
  - DO NOT attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous. This will result in reduction of gangrenous contents and subsequent need for laparotomy

Treatment
- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, or for cosmesis; if asymptomatic, can delay surgery. Data has shown that prophylactic surgery does not affect rate of strangulation in ASYMPTOMATIC patients
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

Postoperative Complications
- recurrence (15-20%)
  - risk factors: recurrent hernia, ages >50, smoking, BMI >25, poor preoperative functional status (ASA ≥3 – see Anesthesia, A4), associated medical conditions: T2DM, hyperlipidemia, immunosuppression, and any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/"tension-free" repair
- scrotal hematoma (3%)
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
- nerve entrapment
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein
  - acute leg swelling
- ischemic colitis
- minimally invasive repair for ventral and umbilical hernia

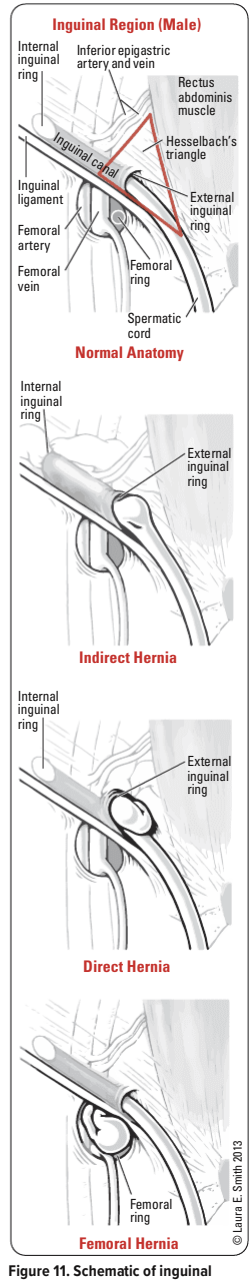


Figure 11. Schematic of inguinal (direct and indirect) and femoral hernias

Groin Hernias

Table 16. Groin Hernias

	Direct Inguinal	Indirect Inguinal	Femoral
Epidemiology	1% of all men	Most common hernia in men and women M>F	Affects mostly females
Etiology	Acquired weakness of transversalis fascia "Wear and tear" Increased intra-abdominal pressure	Congenital persistence of processus vaginalis in 20% of adults	Pregnancy weakness of pelvic floor musculature Increased intra-abdominal pressure
Anatomy	Through Hesselbach's triangle **Medial** to inferior epigastric artery Usually does not descend into scrotal sac	Originates in deep inguinal ring Lateral to inferior epigastric artery Often descends into scrotal sac (or labia majora)	Into femoral canal, below inguinal ligament but may override it Medial to femoral vein within femoral canal
Treatment	Surgical repair	Surgical repair	Surgical repair
Prognosis	3-4% risk of recurrence	<1% risk of recurrence	

Table 17. Superficial Inguinal Ring vs. Deep Inguinal Ring*

Superficial Inguinal Ring	Deep Inguinal Ring
Opening in external abdominal aponeurosis; palpable superior and lateral to pubic tubercle	Opening in transversalis fascia: palpable superior to mid-inguinal ligament
Medial border: medial crus of external oblique aponeurosis	Medial border: inferior epigastric vessels
Lateral border: lateral crus of external oblique aponeurosis	Superior-lateral border: internal oblique and transversus abdominis muscles
Roof: intercrural fibres	Inferior border: inguinal ligament

*see *Basic Anatomy Review, Figure 2, GS3*

Robotic Inguinal vs. Transabdominal Laparoscopic Inguinal Hernia Repair: The RIVAL Randomized Clinical Trial
JAMA Surg. 2020;155(5):380-387
Purpose: To determine whether a robotic approach to inguinal hernia repair results in improved postoperative outcomes compared with the traditional laparoscopic inguinal hernia repairs.
Results: At preoperative, 1 wk and 30 d assessments there were no differences between the groups on wound events, readmissions, pain, or quality of life. However, the robotic approach was associated with increased cost, operative time, and surgeon frustration compared to the laparoscopic approach.
Conclusions: There is no benefit of the robotic approach compared with the laparoscopic approach.

Appendix

Appendicitis

Epidemiology
- 6% of population, M>F (1.4:1)
- 80% between ages 5-35

Pathogenesis
- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecalith, or obstructing neoplasm
  - other causes: parasites or foreign body

Clinical Features
- most reliable feature is progression of signs and symptoms
- low-grade fever (38˚C), rises if perforation
- abdominal pain then anorexia, N/V
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well-localized pain over McBurney's point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
- signs
  - inferior appendix: McBurney's sign (see sidebar), Rovsing's sign (palpation pressure to left abdomen causes McBurney's point tenderness). McBurney's sign is present whenever the opening of the appendix at the cecum is directly under McBurney's point; therefore McBurney's sign is present even when the appendix is in different locations
  - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
  - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)

Complications
- perforation (especially if >24 h duration)
- abscess, phlegmon
- sepsis

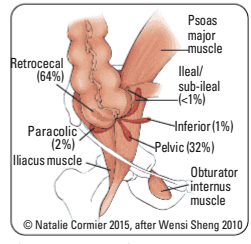


Figure 12. Appendix anatomy

McBurney's Sign
Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side

Investigations
- laboratory
  - mild leukocytosis with left shift (may have normal WBC counts)
  - higher leukocyte count with perforation
  - β-hCG to rule out ectopic pregnancy
  - urinalysis
- imaging
  - U/S: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/NPV/PPV 98%)
  - CT scan: thick wall, enlarged (>6 mm), wall enhancement, appendicolith, and inflammatory changes – overall accuracy 94-100%, optimal investigation

Treatment
- hydrate, correct electrolyte abnormalities
- appendectomy (gold standard)
  - laparoscopic is standard
  - complications: intra-abdominal abscess, appendiceal stump leak
  - perioperative antibiotics: cefazolin + metronidazole; if uncomplicated, perioperative dose is adequate
- consider treatment with postoperative antibiotics for perforated appendicitis
- for patients who present with an abscess (palpable mass or phlegmon on imaging and often delayed diagnosis with symptoms for >4-5 d), consider radiologic drainage + antibiotics x14 d ± interval appendectomy once inflammation has resolved = (controversial)
- medical management with antibiotic therapy should be reserved for those who are unfit for or refuse surgery
- colonoscopy in those >50 yr to rule out concurrent etiology (neoplasm)

Antibiotics versus Appendectomy for Acute Appendicitis - Longer-Term Outcomes
N Engl J Med 2021;385(25):2395. Epub 2021 Oct 25.
Purpose: Compare the efficacy of antibiotics vs. an appendectomy for acute appendicitis with respect to long-term outcomes.
Method: Randomized trial comparing antibiotic treatment with appendectomy in patients with appendicitis.
Results: The 30-day general health status of patients treated with antibiotics was comparable to the appendectomy group. However, 29 percent of medically-treated patients required appendectomy by 90 d. Longer-term data from this trial now confirm high rates of subsequent appendectomy after initial medical therapy: 40 percent at one year, 46 percent at two years, and 49 percent at three and four years.
Conclusions: Surgery should continue to be recommended for uncomplicated appendicitis and antibiotic therapy should be reserved for those who are medically unfit for or decline surgery.

Prognosis
- mortality rate: 0.09-0.24%

Inflammatory Bowel Disease
- see Gastroenterology, G22

Principles of Surgical Management
- medical management remains first line, but surgery can alleviate symptoms, address complications, and improve quality of life
- conserve bowel: resect as little as possible to avoid short gut syndrome
- perioperative management
  - optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  - hold immunosuppressive therapy preoperative, provide preoperative stress dose of corticosteroid; if patient had recent steroid therapy, taper steroids postoperative
  - VTE prophylaxis: LMWH or heparin (IBD patients at increased risk of thromboembolic events)

Crohn's Disease
- see Gastroenterology, G23

Crohn's 3 Major Patterns
- Ileocecal 40% (RLQ pain, fever, weight loss)
- Small intestine 30% (especially terminal ileum)
- Colon 25% (diarrhea)

Findings in Crohn's
- "Cobblestoning" on mucosal surface due to edema and linear ulcerations
- "Skip lesions": normal mucosa in between
- "Creeping fat": mesentery infiltrated by fat
- Granulomas: 25-30%

Treatment
- surgery is for symptom management; it is NOT curative, but over lifetime ~70% of Crohn's patients will have surgery
- indications for surgical management
  - failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), and perianal disease
- surgical procedures
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, or fistula
  - surgery should be attempted in the elective setting ideally off steroids
- resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

Complications of Treatment
- anastomotic leak
- dehydration
- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

Prognosis
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr

Ulcerative Colitis

- see Gastroenterology, G25

Treatment
- indications for surgical management
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per yr after 10 yr of disease)
- surgical procedures
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
  - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

Complications of Treatment
- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

Prognosis
- mortality: 5% over 10 yr
- total proctocolectomy will eliminate risk of cancer
- perforation of the colon is the leading cause of death from UC

LARGE INTESTINE

Large Bowel Obstruction

Mechanical Large Bowel Obstruction

Etiology

Table 18. Common Causes of LBO

Intraluminal	Intramural	Extramural
Constipation	Adenocarcinoma	Volvulus
Foreign bodies	Diverticulitis (edema, stricture)	Adhesions
	IBD stricture	Hernias (sigmoid colon in a large groin hernia)
	Radiation stricture	

Top 3 Causes of LBO (in order)
- Cancer (>60%)
- Volvulus (10-15%)
- Diverticulitis (10%)

In a patient with a clinical LBO consider impending perforation when:
- Cecum ≥12 cm in diameter
- Tenderness present over cecum

Clinical Features (unique to LBO)
- open loop (10-20%)
  - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical features similar to SBO
- closed loop (80-90%) (dangerous)
  - competent ileocecal valve, resulting in proximal and distal occlusions
  - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

Investigations
- CBC with differential, BUN, electrolyte panel, creatinine, CEA if patient is suspected to have malignancy, and lactate for level of ischemia
- imaging: AXR and CT scan

Treatment
- supportive management: IV fluids, gastrointestinal decompression
- surgical intervention (75% of cases)
  - volvulus: initial decompression with flexible sigmoidoscopy, operative reduction or sigmoid resection dependent on severity
  - colorectal obstruction: ostomy alone (fecal diversion), colectomy with primary anastomosis, or Hartmann procedure
- may pursue stenting as a bridge to surgery or palliation

Prognosis
- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality

Table 19. Bowel Obstruction vs. Paralytic Ileus

	SBO	LBO	Paralytic Ileus
N/V	Early, may be bilious	Late, may be feculent	Present
Abdominal Pain	Colicky	Colicky	Minimal or absent
Abdominal Distention	+ (prox SBO), ++ (distal SBO)	++	+
Constipation	+	+	+
Bowel Sounds	Normal, increased Absent if secondary ileus (delayed presentation)	Normal, increased (borborygmi) Absent if secondary ileus (delayed presentation)	Decreased, absent
AXR Findings	Air-fluid levels "Ladder" pattern (plicae circulares) Proximal distention (>3 cm) + no colonic gas	Air-fluid levels "Picture frame" appearance Proximal distention + distal decompression No small bowel air if competent ileocecal valve Coffee bean sign (sigmoid volvulus)	Air throughout small bowel and colon

Functional Large Bowel Obstruction: Colonic Pseudo-Obstruction (Ogilvie's Syndrome)

Definition
- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- exact mechanism unknown, likely autonomic motor dysregulation

Associations
- most common: trauma, infection, and cardiac (MI, CHF)
- disability (long-term debilitation, chronic disease, bed-bound nursing home patients, and paraplegia), drugs (narcotic use, laxative abuse, and polypharmacy), and other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, and diffuse carcinomatosis)

Clinical Features
- classically presents with abdominal distention (acute or gradual over 3-7 d)
- abdominal pain, N/V, constipation or diarrhea
- watch out for fever, leukocytosis, and presence of peritoneal signs (suggestive of colonic ischemia or perforation)

Investigations
- AXR: cecal dilatation (if diameter ≥12 cm, increased risk of perforation)

Treatment
- treat underlying cause
- NPO, NG tube
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), or surgical (ostomy/resection)
- surgery (extremely rare): if perforation, ischemia, or failure of conservative management

Prognosis
- most resolve with conservative management

Diverticular Disease

Definitions
- diverticulum: abnormal outpouching from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

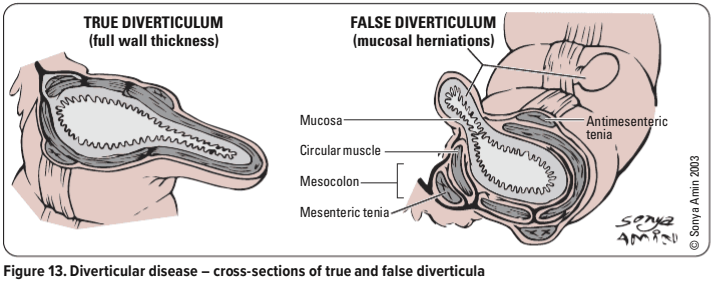


Figure 13. Diverticular disease – cross-sections of true and false diverticula

Diverticulosis

Epidemiology
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

Diverticulosis vs. Diverticulitis
Diverticulosis represents the presence of diverticuli (bulging pouches) within the colonic wall, whereas diverticulitis is the inflammation of one or more diverticuli

Pathogenesis
- risk factors
  - lifestyle: diet (low-fibre, high fat, red meat), inactivity, and obesity
  - muscle wall weakness from aging and illness (e.g. Ehlers-Danlos, Marfan's)
- high intraluminal pressures cause outpouching to occur at points of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer leading to an increased risk of hemorrhage

Clinical Features
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications:
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive LGIB
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, and abdominal pain

Treatment
- uncomplicated diverticulosis: high fibre, education
- diverticular bleed
  - initially workup and treat as any LGIB
  - if hemorrhage does not stop, resect involved region

Diverticulitis

Epidemiology
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

Pathogenesis
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula, or obstruction can ensue
- poor containment results in free perforation and peritonitis

Clinical Features

- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, N/V, and urinary symptoms (with adjacent inflammation)
- low-grade fever, mild leukocytosis, and occult or gross blood in stool rarely coexist with acute diverticulitis
- complications (25% of cases)
  - abscess: palpable, tender abdominal mass
  - fistula: colovesical (most common), coloenteric, colovaginal, and colocutaneous
  - colonic obstruction: related to colonic strictures secondary to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
- recurrent attacks rarely lead to peritonitis

Investigations

- CT scan (test of choice)
  - very useful for assessment of severity and prognosis (97% sensitive, 99% specific)
  - usually done with rectal contrast
  - increased soft tissue density within pericolic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), and fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- AXR, upright CXR
  - localized diverticulitis (ileus, thickened wall, SBO, and partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- colonoscopy or barium enema and flexible sigmoidoscopy (elective evaluation)
  - establish extent of disease and rule out other diagnoses (polyps and malignancy) AFTER resolution of acute episode

Treatment

- uncomplicated: conservative management
- outpatient: clear fluids only until improvement. Avoid treatment with antibiotics for those with uncomplicated acute diverticulitis
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, or fail to improve with outpatient management
  - treat with NPO, IV fluids, and IV antibiotics (e.g. IV ceftriaxone + metronidazole)
- image-guided (CT) percutaneous drainage of abscesses reduces the urgency of surgical resection in most patients
- surgery:
  - indications:
    - unstable patient with peritonitis
    - Hinchey stage 3-4 (see *Table 20*)
    - after 1 attack if immunosuppressed
    - consider if recurrent episodes of diverticulitis (≥3); recent trend is toward conservative management of recurrent mild/moderate attacks
  - procedures:
    - Hartmann resection (for unstable or complex cases)
    - colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo
  - for more stable patients with Hinchey stage 3 and 4 acute diverticulitis: colonic resection, primary anastomosis + diverting loop ileostomy is becoming more common, with benefits for mortality and morbidity
  - for Hinchey stage 3: laparoscopic peritoneal lavage with drain placement near the affected colon, in addition to 4 antibiotics (NO resection), has been proposed
  - complications: perforation, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management

Prognosis

- mortality rates: 6% for purulent peritonitis, 35% for feculent peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

Efficacy and Safety of Nonantibiotic Outpatient Treatment in Mild Acute Diverticulitis (DINAMO-study): A Multicentre, Randomised, Open-label, Noninferiority Trial
Ann Surg 2021;274(5):e435
Background: In recent years, it has shown no benefit of antibiotics (ATB) in the treatment of uncomplicated Acute Diverticulitis in hospitalized patients.
Methods: Prospective, multicentre, open-label, noninferiority, randomized controlled trial.
Results: Differences in hospitalization rates, revisits, and poor pain control at 2 d follow-up were within the non-inferiority margin.
Conclusions: Nonantibiotic outpatient treatment of mild AD is safe and effective and is not inferior to current standard treatment.

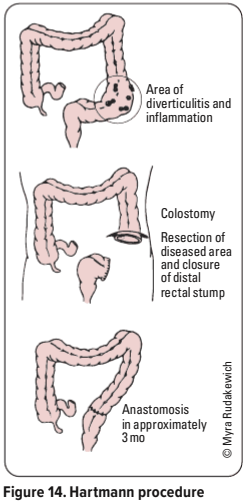

Area of diverticulitis and inflammation
Colostomy
Resection of diseased area and closure of distal rectal stump
Anastomosis in approximately 3 mo
© Myra Rudakewich

Figure 14. Hartmann procedure

Table 20. Hinchey Staging and Treatment for Diverticulitis

Hinchey Stage	Description	Acute Treatment
1	Phlegmon/small pericolic abscess	Medical
2	Large abscess/fistula	Medical, abscess drainage ± resection with primary anastomosis
3	Purulent peritonitis (ruptured abscess)	Resection or Hartmann procedure
4	Feculent peritonitis	Hartmann procedure

Colorectal Neoplasms

Colorectal Polyps

Definition
- polyp: protuberance into the lumen of normally flat colonic mucosa
  - sessile (flat) or pedunculated (on a stalk)

Epidemiology
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70; M>F

Clinical Features
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, and mucus
- usually detected during routine endoscopy or familial/high-risk screening

Pathology
- non-neoplastic/non-adenomatous
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
    - malignant risk due to associated adenomas (large bowel)
    - low malignant potential → most spontaneously regress or autoamputate
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, and carcinoids
- neoplastic/adenomatous
  - adenomas: premalignant, considered carcinoma *in situ* if high-grade dysplasia
    - may contain invasive carcinoma ("malignant polyp" – 3-9%): invasion into submucosa
    - malignant potential related to histological type: villous > tubulovillous > tubular

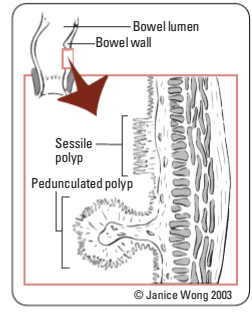


Figure 15. Sessile and pedunculated polyps

Table 21. Characteristics of Tubular vs. Villous Polyps

	Tubular	Villous
Incidence	Common (60-80%)	Less common (10%)
Size	Small (<2 cm)	Large (usually >2 cm)
Attachment	Pedunculated	Sessile
Malignant Potential	Lower	Higher
Distribution	Even	Left-sided predominance

Investigations
- colonoscopy with biopsy/resection (gold standard)
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscopy (if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy)

Treatment
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- indications for segmental resection for malignant polyps: 1) lymphovascular invasion; 2) tumour budding; 3) positive resection margin; 4) poorly differentiated cells; 5) evidence of regional or distant metastases on staging
  - most of these cases are usually discussed at multidisciplinary tumour boards
- follow-up endoscopy:
  - every 5 yr: if low-risk polyp (<10 mm tubular adenoma or <10 mm sessile serrated without dysplasia)
  - every 3 yr: if high-risk polyp (3-10 tubular adenomas, >10 mm tubular or serrated polyp, adenoma with villous features or high grade dysplasia, or sessile serrated with dysplasia)

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS

Epidemiology
- accounts for <1% of colorectal cancers, affects males and females equally

Pathogenesis
- autosomal dominant inheritance, mutation in adenomatous polyposis coli (APC) gene

Clinical Features
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40's in attenuated FAP)
- virtually 100% lifetime risk of colon cancer (due to number of polyps)
- extracolonic manifestations
  - bile duct, pancreas, stomach, thyroid (large benign multinodular goitre), adrenal glands, and small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
- variants
  - Gardner's syndrome: FAP + extra-intestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
  - Turcot syndrome: FAP + central nervous system tumours (childhood cerebellar medulloblastoma)

Investigations
- genetic testing (80-95% sensitive, 99-100% specific)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy, consider surgery, and consider upper endoscopy to evaluate for periampullary tumours

Treatment
- surgery indicated by ages 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

Referral Criteria for Genetic Screening for APC
- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 yr)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER – LYNCH SYNDROME

Epidemiology
- most common inherited colorectal cancer susceptibility syndrome and accounts for 3% of colorectal cancer diagnoses

Pathogenesis
- autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1, PMS2) resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all CRCs

Clinical Features
- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr, lifetime risk 70-80%; M>F
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome → high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel, adrenal)

Diagnosis
- Amsterdam Criteria ("3-2-1 rule")
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr
  - FAP is excluded
- genetic testing (80% sensitive)
  - refer individuals for genetic screening if they fulfill either the Amsterdam Criteria or the revised Bethesda Criteria
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

Treatment
- total colectomy and ileorectal anastomosis with annual proctoscopy

Revised Bethesda Criteria for HNPCC and Microsatellite Instability (MSI)
Tumours from individuals should be tested for MSI in the following situations:
- Colorectal cancer diagnosed in a patient who is <50 yr
- Presence of synchronous, metachronous, colorectal, or other HNPCC-associated tumours, regardless of age
- Colorectal cancer with the MSI-H histology diagnosed in a patient who is <60 yr
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed <50 yr
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

Elderly persons who present with iron-deficiency anemia should be investigated for colon cancer

APR removes distal sigmoid colon, rectum, and anus; permanent end colostomy required
LAR removes distal sigmoid and rectum with anastomosis of distal colon to distal rectum/anus

Colorectal Carcinoma

Epidemiology
- 3rd most common cancer (lung > breast > colon), 2nd most common cause of cancer death

Risk Factors
- most patients have no specific risk factors
- ages >50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, or family history of CRC
- colonic conditions
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - previous colorectal, gonadal, or breast cancer
- diet (increased fat, red meat, decreased fibre) and smoking
- DM and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

Pathogenesis
- adenoma-carcinoma sequence; rarely arise de novo

Clinical Features
- often asymptomatic
- hematochezia/melena, abdominal pain, and change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, and obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread
  - direct extension, lymphatic, and hematogenous (liver most common, lung, bone, and brain; tumour of distal rectum → IVC → lungs)
  - peritoneal seeding: ovary and Blumer's shelf (pelvic cul-de-sac)

Table 22. Clinical Features of CRC

	Right Colon	Left Colon	Rectum
Frequency	25%	35%	30%
Pathology	Exophytic lesions with occult bleeding	Annular, invasive lesions	Ulcerating
Symptoms	Weight loss, weakness, rarely obstruction	Constipation ± overflow (alternating bowel patterns), abdominal pain, decreased stool calibre, rectal bleeding	Obstruction, tenesmus, rectal bleeding
Signs	Fe-deficiency anemia, RLQ mass (10%)	BRBPR, LBO	Palpable mass on DRE, BRBPR

Investigations
- colonoscopy (gold standard): look for synchronous lesions (3-5% of patients)
  - if a patient is FOBT positive, has microcytic anemia, or has a change in bowel habits → colonoscopy
  - alternative: air contrast barium enema ("apple core" lesion) + sigmoidoscopy
- laboratory: CBC, U/A, LFTs, CEA (preoperative for baseline, >5 ng/mL have worse prognosis)
- staging: CT chest/abdomen/pelvis; bone scan and CT head only if lesions suspected
- rectal cancer: pelvic MRI or endorectal U/S to determine T and N stage

Table 23. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/UICC 8th edition)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
Tx	Primary tumour cannot be assessed	**Nx**	Regional nodes cannot be assessed	**M0**	No distant metastasis
T0	No primary tumour found	**N0**	No regional node metastasis and no tumour deposits	**M1a**	Distant metastasis to 1 organ or site and no peritoneal metastasis
Tis	Carcinoma *in situ*, limited to intraepithelial or invasive lamina propria	**N1a**	Metastasis in 1 regional node	**M1b**	Distant metastasis to >1 (2 or more organs sites) and no peritoneal metastasis
T1	Invasion into submucosa	**N1b**	Metastasis in 2-3 regional nodes	**M1c**	Metastasis to peritoneal surface
T2	Invasion into muscularis propria	**N1c**	No regional node metastasis; tumour deposits were submucosal, mesangial or peritoneum-covered para-colorectal tissue		
T3	Invasion through muscularis propria and into pericolorectal tissues	**N2a**	Metastasis in 4-6 regional nodes		
T4a	Invasion through visceral peritoneum	**N2b**	Metastasis in ≥7 regional nodes		
T4b	Invasion or adherent to other organs or structures				

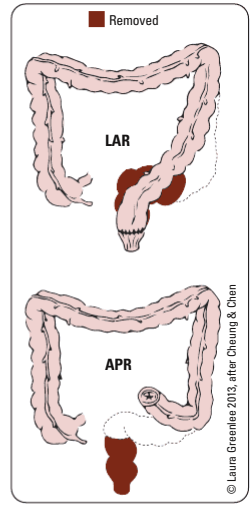


Figure 16. APR vs. LAR

5 Year Survival Rates for CRC

Stage	20-64 yr	≥65 yr
I	95.2%	89.1%
IIA	89.6%	84.4%
IIB	67.6%	55%
IIIA	91.3%	85.1%
IIIB	76.9%	64.6%
IIIC	61.8%	45.5%
IV	14.2%	7.4%

Preoperative vs. Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial after a Median Follow-Up of 11 Yr

J Clin Oncol 2012;30:1926-1933

Background: The CAO/ARO/AIO-94 trial (published 2004) recommended preoperative chemoradiotherapy (CRT) as standard treatment for locally advanced rectal cancer. However, no survival benefit was shown after median follow-up of 46 mo, and this study reports long-term effects.

Methods: Patients with stage II to III rectal cancer (n=799) were randomly assigned to preoperative (n=404) or postoperative CRT (n=395) with fluorouracil (FU), radiation, and adjuvant FU chemotherapy, in addition to total mesorectal excision surgery. Follow-up was designed to assess long-term overall survival as the primary endpoint and cumulative incidence of local and distant relapses as well as disease-free survival as secondary endpoints.

Results: 10 yr incidence of local relapse was significantly lower in the preoperative CRT group than in the postoperative group (7.1% vs. 10.1%, P=0.048). Overall survival at 10 yr was similar at ~60% for patients treated with preoperative or postoperative CRT (P=0.85). Disease-free survival rates at 10 yr was similar at ~68% for patients treated with preoperative or postoperative CRT (P=0.54). No significant difference was detected for 10 yr incidence of distant metastases (preoperative CRT 29.8% vs. postoperative CRT 29.6%, P=0.9).

Conclusion: There is long-term reduction in local recurrence of stage II to III rectal cancer with preoperative chemotherapy, but no improvement in overall survival or distant recurrence of disease.

Treatment
- colon cancer
  - wide surgical resection of lesion according to vascular distribution and regional lymphatic drainage; usually colectomy with primary anastomosis
  - curative: wide resection of lesion (5 cm margins) with nodes (>12) and mesentery
  - care is taken to not spread tumour by unnecessary palpation
  - adjuvant chemotherapy (oxaliplatin-based) for stage III and is considered in select stage II patients
  - palliative: if distant spread, local control for hemorrhage or obstruction
- metastatic lesions confined to the liver can be resected with curative intent
- rectal cancer
  - choice of operation depends on individual case
    - LAR: curative procedure of choice if adequate distal margins (~2 cm); uses technique of total mesorectal excision
      - APR: if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus permanent end colostomy required
    - transanal minimally invasive surgery (TAMIS): local excision for select T1 lesions only
  - palliative procedures involve proximal diversion with an ostomy for obstruction and radiation for bleeding or pain
  - combined neoadjuvant chemoradiation therapy followed by postoperative adjuvant chemotherapy for stages II and III

Follow-Up
- stage I: mixed recommendations; either routine colonoscopy or screening like stage II & III
- stage II & III: regular follow-up q3-6 mo for 3 yr, then q6 mo until 5 yr, with regular measurement of serum CEA for at least 3 yr; annual CT chest/abdo/pelvis for at least 3 yr; colonoscopy at 1, 3, and 5 yr
- stage IV: no data on surveillance strategy

Other Conditions of the Large Intestine

Angiodysplasia

Definition
- vascular malformation: focal submucosal venous dilatation and tortuosity

Clinical Features
- most frequently in right colon of patients >60 yr
- predisposition in end-stage renal disease, and Von Willebrand disease, and aortic stenosis
- bleeding typically intermittent, rarely massive, and not usually hypotensive (melena, anemia, and occult blood positive stools)
- >90% of cases cease bleeding spontaneously

Investigations
- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, and delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

Treatment
- none if asymptomatic
- cautery, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

Volvulus

Definition
- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), and splenic flexure (2%)
  - elderly >70 yr (sigmoid), adult 40-60yr (cecal), and neonates and infants (midgut)
- 5-10% of large bowel obstructions; 25% of intestinal obstructions during pregnancy

Risk Factors
- age (50% of patients >70 yr: stretching/elongation of bowel with age)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, and institutionalization (less frequent evacuation of bowels)
- megacolon
- intestinal bands/adhesions

Cecal Volvulus
AXR: Central cleft of "coffee bean" sign points to RLQ

Sigmoid Volvulus
AXR: Central cleft of "coffee bean" sign points to LLQ
Barium enema: "ace of spades" or "bird's beak" sign

Clinical Features
- symptoms due to bowel obstruction (see *Large Bowel Obstruction, GS37*) or intestinal ischemia (see *Intestinal Ischemia, GS31*)
- colicky abdominal pain, persistence of pain between spasms, abdominal distention, and vomiting

Investigations
- AXR (classic findings): "omega," "bent inner-tube," "coffee-bean" signs, multiple air-fluid levels
- barium/Gastrografin® enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT: "whirl pattern" of mesenteric vessels twisting about the volvulus axis
  - barium contrast and colonoscopy are contraindicated due to risk of perforation

Treatment
- initial supportive management same as initial management for bowel obstruction (see *Large Bowel Obstruction, GS37*)
- cecum
  - colonoscopic detorsion and decompression; successful 15-20% of cases
  - surgical
    - right colectomy + ileotransverse colonic anastomosis
- sigmoid
  - decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
  - subsequent elective surgery recommended (50-70% recurrence)
  - surgical
    - surgical resection with or without primary anastomosis
    - indications for urgent surgical management: strangulation, perforation, or unsuccessful endoscopic decompression

Toxic Megacolon

Pathogenesis
- extension of inflammation into smooth muscle layer causing paralysis and leading to nonobstructive colonic dilatation
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

Etiology
- IBD (UC > Crohn's disease)
- infectious colitis: bacterial (*C. difficile, Salmonella, Shigella*, and *Campylobacter*), viral (cytomegalovirus), and parasitic (E. histolytica)

Clinical Features
- infectious colitis usually presents for >1 wk before colonic dilatation
- diarrhea ± blood (sudden improvement of diarrhea may signify onset of megacolon)
- abdominal distention, tenderness, ± local/general peritoneal signs (suggests perforation)
- triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, and anticholinergics), barium enema, and colonoscopy

Diagnostic Criteria
- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon >6 cm, and
- three of: fever, HR >120, WBC >10.5, anemia and
- one of: dehydration, electrolyte disturbances, hypotension, or altered LOC

Investigations
- CBC (leukocytosis with left shift and anemia from bloody diarrhea), electrolytes, elevated c-reactive protein, and ESR
  - metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease severity and possible complications (i.e. abscess, perforation, ascending pylephlebitis)

Treatment
- NPO, NG tube, stop constipating agents, correct fluid and electrolyte abnormalities, and transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis and anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD and metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management)
  - worsening or persisting toxicity or dilation after 48-72 h
  - severe hemorrhage, perforation
  - high lactate and WBC, especially for *C. difficile*
- procedure: subtotal colectomy + end ileostomy (possible re-anastomosis later)

Use caution when giving antidiarrheal agents, especially with bloody diarrhea

Prognosis
- 25-30% mortality

Fistula

Definition
- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, and entero-enteric)

Etiology
- foreign object erosion (e.g. drainage tube, gallstone, graft)
- inflammatory states (e.g. infection, IBD (Crohn's > UC), and diverticular disease)
- iatrogenic/surgery (e.g. postoperative anastomotic leak and radiation)
- congenital, trauma
- neoplastic

Why Fistulae Stay Open

FRIENDO
Foreign body
Radiation
Infection
Epithelialization
Neoplasm
Distal obstruction (most common)
Others: increased flow; steroids (may inhibit closure, usually will not maintain fistula)

Investigations
- U/S, CT scan, fistulogram
- measure amount of drainage from fistula

Treatment
- decrease secretion: octreotide/somatostatin/omeprazole
- surgical intervention: dependent upon etiology (for non-closing fistulas)

Stomas

Definition
- an opening of the GI tract onto the surface of the abdomen wall
  - end stomas: the proximal end of the GI tract forms the stoma and the distal end of the GI tract is not part of the stoma
  - loop stomas: a loop of the GI tract is brought up to the skin and the antimesenteric surface of the bowel is matured as a stoma

Colostomy/Ileostomy
- Connection of proximal limb of colon or ileum to abdominal wall skin
- Mucous fistula
- Connection of distal limb of resection margin to abdominal wall skin
- Ileal Conduit
- Connection of bowel to ureter proximally and abdominal wall distally to drain urine

Ileostomy
- usually positioned in RLQ; ileum is brought through rectus abdominis muscles
- indications: after proctocolectomy for UC, some cases of Crohn's disease or familial polyposis
- conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
- continent ileostomy: reservoir is constructed from distal ileum (ileal pouch anal anastomosis)

Colostomy
- indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
- colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
- most common permanent colostomy is a sigmoid colostomy (expels stool/digital removal of feces)
- chronic paracolostomy hernia is a common complication

Complications (10%)
- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output), which may lead to fluid, electrolyte, and nutritional imbalances

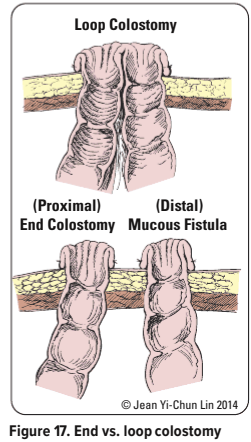


Figure 17. End vs. loop colostomy

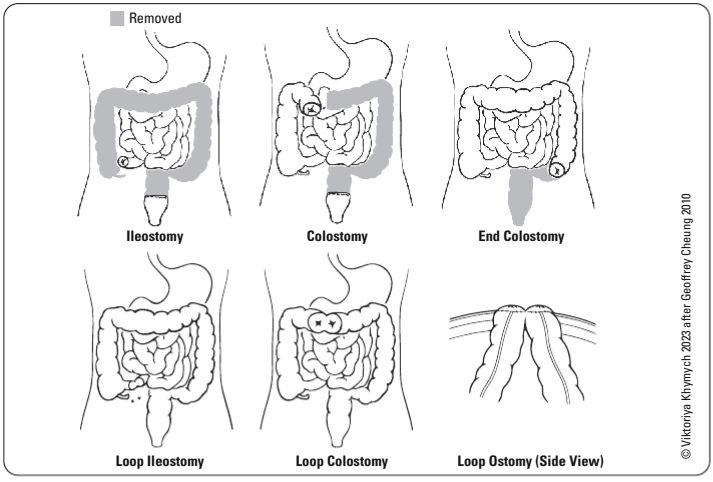


Figure 18. Ostomies

Anorectum

Hemorrhoids

Etiology
- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
- internal: superior hemorrhoidal veins, above dentate line, portal circulation
- external: inferior hemorrhoidal veins, below dentate line, systemic circulation

Risk Factors
- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal HTN, heavy lifting

Clinical Features and Treatment
- internal hemorrhoids
  - engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  - painless rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, and rectal fullness
    - **1st degree**: bleed but do not prolapse through the anus
      - treatment: high fibre/bulk diet, sitz baths, steroid cream (short course), pramoxine (Anusol®), phlebotonics, rubber band ligation, sclerotherapy, and photocoagulation
    - **2nd degree**: bleed, prolapse with straining, and spontaneous reduction
      - treatment: rubber band ligation, and photocoagulation
    - **3rd degree**: bleed, prolapse, and require manual reduction
      - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
    - **4th degree**: bleed, permanently prolapsed, and cannot be manually reduced
      - treatment: closed hemorrhoidectomy
- external hemorrhoids
  - dilated venules usually mildly symptomatic
    - pain after bowel movement, associated with poor hygiene
    - medical treatment: dietary fibre, stool softeners, steroid cream (short course), pramoxine (Anusol®), phlebotonics, and avoid prolonged straining
  - thrombosed hemorrhoids are very painful
    - resolve within 2 wk, may leave excess skin = perianal skin tag
    - treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment
- indications for referral for endoscopic evaluation: history of melena, postural vital sign abnormalities, constitutional symptoms suggestive of malignancy, and family history of inherited colorectal syndromes

Prevention
- high fibre diets, prevent constipation, stool softeners

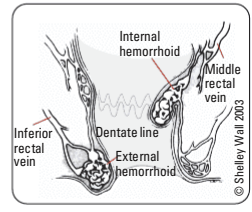


Figure 19. Hemorrhoids

Always rule out more serious causes (e.g. colon cancer or anal canal cancer) in a person with hemorrhoids and rectal bleeding

Band ligation can be done as outpatient

External hemorrhoids will often recur

Table 24. Signs and Symptoms of Internal vs. External Hemorrhoids

Internal Hemorrhoids	External Hemorrhoids
Painless BRBPR	Sudden severe perianal pain
Rectal fullness or discomfort	Perianal mass
Mucus discharge	

Anal Fissures

Definition
- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline because posteromedial area is poorly perfused, 10% anterior midline
- if off midline: consider other possible causes such as IBD, STIs, TB, leukemia, or anal carcinoma
- repetitive injury cycle after first tear
  - sphincter spasm occurs preventing edges from healing and leads to further tearing
  - ischemia may ensue and contribute to chronicity

Etiology
- local trauma: constipation, irritation, diarrhea, vaginal delivery, anal intercourse
- secondary to: Crohn's disease, granulomatous diseases, malignancy, communicable diseases
- further tearing by internal anal sphincter spasm and hypertonicity

Clinical Features
- acute fissure
  - very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - treatment is conservative: stool softeners, bulking agents, and sitz baths (heals 90%)
- chronic fissure (anal ulcer)
  - triad: fissure, sentinel skin tags, and hypertrophied papillae
  - treatment
    - stool softeners, increased fibre intake, and sitz baths
    - topical nitroglycerin or calcium channel blocker (nifedipine or diltiazem): increases local blood flow, promotes healing, and relieves sphincter spasm
    - lateral internal anal sphincterotomy (most effective): relieves sphincter spasm to increase blood flow and promote healing; reserved for medically-refractory cases due to 5% chance of fecal incontinence
    - alternative treatment: botulinum toxin A; inhibits release of acetylcholine (ACh), reducing sphincter spasm

Prevention
- avoid diarrhea or constipation, avoid straining during defecation, high fibre diet, adequate fluids

Anorectal Abscess

Definition
- infection typically originating within an obstructed anal crypt which forms an abscess
- common bacterial: *E. coli, Proteus, Streptococci, Staphylococci, Bacteroides*, and anaerobes

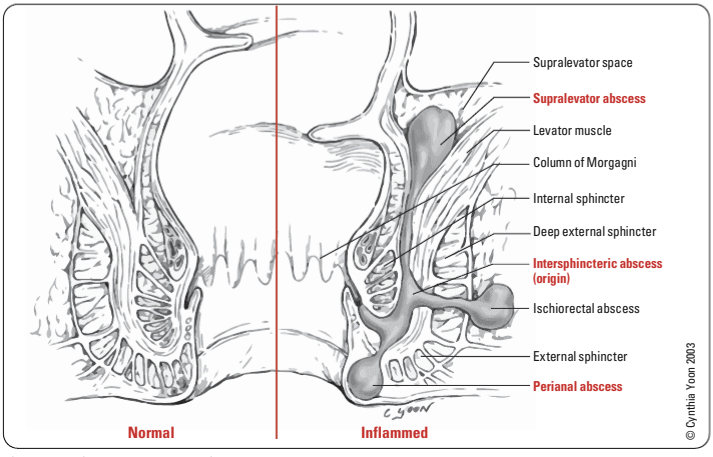


Figure 20. Different types of perianal abscesses

Clinical Features
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator), or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

Treatment
- I&D
  - curative in 50% of cases
  - 50% develop anorectal fistulas
- may require antibiotics if patient has DM, a heart murmur, or cellulitis

Recurrent perianal abscesses is associated with Crohn's disease

Antibiotics are not typically helpful in the treatment of perianal abscesses

Fistula-In-Ano

Definition
- fistula from anal canal to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

Etiology
- see *Fistula, GS46*
- same processes that lead to the formation of an anal abscess
- other causes: postoperative, trauma, anal fissure, malignancy, and radiation proctitis

Clinical Features
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract
- inflamed or excoriated perianal skin
- MRI best imaging but can use CT or U/S depending on location

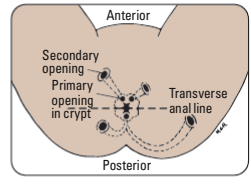


Figure 21. Goodsall's rule

Treatment
- identification
  - internal opening
    - Goodsall's rule: fistulas originating anterior to a transverse line through the anus will have a straight course and exit anteriorly, whereas those originating posterior to the transverse line will begin in the midline and have a curved tract
  - fistulous tract
    - probing or fistulography under anesthesia
- surgery
  - primary fistulotomy: unroof tract from external to internal opening, allows drainage, heals by secondary intention
    - best treatment for low lying fistula (does not involve external sphincter)
  - staged fistulotomy with Seton (rubber band or suture) placed through tract
    - used for high lying fistula (involves external sphincter)
    - promotes drainage, fibrosis, and decreases incidence of incontinence
    - delineates anatomy and usually done to spare muscle
  - ligation of intersphincteric fistula tract (LIFT) procedure
    - access fistula between sphincter muscles, sparing them
  - endoanal advancement flaps

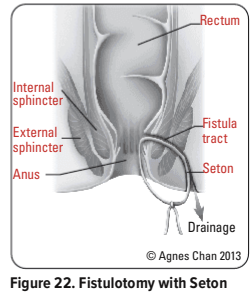


Figure 22. Fistulotomy with Seton suture

Postoperative
- sitz baths, irrigation, and packing to ensure healing proceeds from inside to outside

Complications
- recurrence
- rarely fecal incontinence

Pilonidal Disease

Definition
- pilo = hair, nidal = nest; cyst or abscess near or on the intergluteal cleft of the sacrococcygeal area containing hair and skin debris

Epidemiology
- occurs most frequently in young men ages 15-35; rare in >50 yr

Etiology
- obstruction of the hair follicles in this area → formation of cysts, sinuses, or abscesses
- associated with occupations that require prolonged sitting, obesity, and high amounts of body hair

Clinical Features
- asymptomatic or chronically itchy until acutely infected, then pain/tenderness, purulent discharge, and increased moisture near the tailbone

Treatment
- acute abscess
  - I&D (often performed by primary care physicians)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery
  - indication: failure of healing after I&D, recurrent disease, or complex disease
  - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention (vac dressing), primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

Rectal Prolapse

Definition
- protrusion of some or all of rectal mucosa through external anal sphincter

Epidemiology
- extremes of ages: <5 yr and >50 yr
- 85% women

Etiology
- lengthened attachment of rectum secondary to constant straining
- 2 types
  1. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  2. true/complete (most common): full-thickness extrusion of rectal wall, concentric folds in:
     - 1st degree: prolapse includes mucocutaneous junction
     - 2nd degree: without involvement of mucocutaneous junction
     - 3rd degree (internal intussusception): prolapse is internal, concealed, or occult

Risk Factors
- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility e.g. chronic constipation
- multiparity
- weak pelvic floor

Clinical Features
- extrusion of mass with increased intra-abdominal pressure
- difficulty in bowel regulation
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration, and constant soiling
- may be associated with urinary incontinence or uterine prolapse
- pain is not common

Treatment
- type I
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- type II
  - conservative: reduce if possible
  - surgery: abdominal, perineal, and trans-sacral approaches

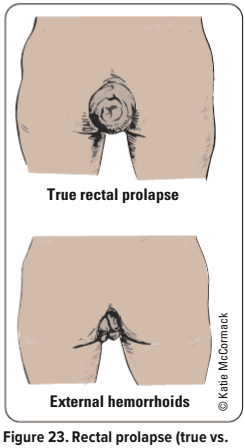


Figure 23. Rectal prolapse (true vs. false)

Anal Neoplasms

ANAL CANAL

Squamous Cell Carcinoma of Anal Canal (Distal to Dentate Line)
- most common tumour of anal canal (75%)
- anus prone to human papillomavirus (HPV) infection, therefore at risk for anal squamous intraepithelial lesions (ASIL)
  - high-grade squamous intraepithelial lesion (HSIL) and low-grade squamous intraepithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, and pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5 yr survival

Malignant Melanoma of Anal Canal

- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- occasionally an incidental finding in pathological evaluation of an anal specimen
- clinical features: bleeding, mass anorectal pain, change in bowel habits, pigmented in one third cases, regional lymph node involvement
- treatment: wide excision or APR ± chemoradiation
- prognosis: <5% 5 yr survival

ANAL MARGIN

- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen's disease (SCC in situ), and Paget's disease

Liver

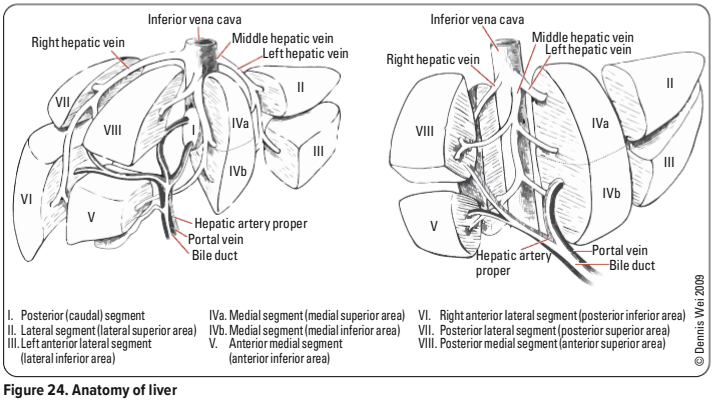


Figure 24. Anatomy of liver

Liver Cysts

Table 25. Characteristics of Liver Cysts

	Simple Cysts	Polycystic Liver Disease	Choledochal Cysts	Hydatid (Cystic Echinococcosis)	Cystadenoma (Premalignant)/ Cystadenocarcinoma
Description	Form from biliary ducts that do not communicate with the intrahepatic biliary tree and contain clear fluid Most common May have multiple cysts Always benign Examples include congenital cysts, Caroli disease, biliary hamartomas, and polycystic liver disease (PCLD)	Several (>20) cysts that replace much of the liver parenchyma Autosomal-dominant condition More common in females	Congenital malformations of the bile ducts High-risk of malignancy Majority present before age 10 Todani classification based on anatomical characteristics within biliary tree	Infection with parasite *Echinococcus granulosus* Associated with exposure to dogs, sheep, horses, pigs, goats, camels, and cattle in Southern Europe, Middle East, Australasia, South America Ingested parasitic eggs hatch in the small intestine, where larvae enter blood and lymph	Cystadenomas are rare cystic neoplasms arising from the bile ducts Cystadenoma is the most common premalignant liver lesion Cystadenocarcinoma is an invasive carcinoma
Clinical Features	Usually asymptomatic Mass effect can cause: dull RUQ pain, N/V, bloating, and/or early satiety	Minority present with acute complications due to cyst rupture, hemorrhage, infection, and compression of adjacent structures Progressive 50% associated with polycystic kidney disease (if over age 60)	Recurrent abdominal pain Intermittent jaundice RUQ mass Cholangitis Symptomatic gallstones Pancreatitis Portal HTN	Usually asymptomatic May have palpable RUQ mass or hepatomegaly Chronic RUQ pain when symptomatic Nausea, fever, and dyspepsia are non-specific symptoms	Upper abdominal mass Abdominal pain Anorexia
Investigations	Labs: some have elevated GGT, CEA, CA 19-9 U/S: Used for diagnosis and follow-up CT: well demarcated lesion that does not enhance with contrast	U/S: cysts are well circumscribed and nonenhancing MRI: more sensitive and specific, used for preoperative planning	Labs: LFT abnormalities U/S CT Transhepatic cholangiography ERCP MRCP	Labs: anti-Echinococcus ab U/S CT: calcified cystic walls Needle biopsy	Labs: cystadenocarcinoma may have elevated LFTs, CEA, or CA 19-9 U/S: anechoic mass with internal septations that are highly echogenic CT MRI MRCP ERCP Need histology for definite diagnosis

Table 25. Characteristics of Liver Cysts

	Simple Cysts	Polycystic Liver Disease	Choledochal Cysts	Hydatid (Cystic Echinococcosis)	Cystadenoma (Premalignant)/ Cystadenocarcinoma
Treatment	Not required unless very large and/or symptomatic Monitor if >4 cm Laparoscopic or open cyst wall removal (unroofing) is established treatment and is usually curative Percutaneous aspiration and ethanol sclerotherapy also an option, but not curative	Symptomatic patients: cyst aspiration with sclerosis, cyst fenestration, hepatic resection, transarterial embolization, and transplantation	Complete excision of cysts Liver resection or transplantation if cystic dilatation involves intrahepatic bile ducts (Caroli's disease)	Systemic chemotherapy: Albendazole (anti-helminthic drug) cure up to 30% Surgical: radical (total pericystectomy, partial hepatectomy, or lobectomy) vs. conservative (drainage or open/ closed cystectomy) Percutaneous: PAIR (puncture, aspiration, injection, re-aspiration)	All complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk
Complications	Hemorrhage, rupture, infection, and biliary obstruction more likely in larger cysts Intracystic hemorrhage is rare and presents with severe abdominal pain		Biliary cirrhosis, portal HTN, cyst rupture, or cholangiocarcinoma Increased risk of biliary malignancy	IVC compression Cyst rupture which can cause fever, pruritus, eosinophilia, biliary colic, jaundice, cholangitis, pancreatitis, or anaphylaxis	Cystadenocarcinoma can invade adjacent tissues and metastasize

Liver Abscesses

Etiology
- types
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *Klebsiella, E. coli, Proteus, Streptococcus, Staphylococcus*, and anaerobes
  - parasitic (amoebic): *Entamoeba histolytica*, Echinococcal cyst
  - fungal: *Candida*
  - sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features
- fever, malaise, chills, anorexia, weight loss, abdominal pain, and nausea
- RUQ tenderness, hepatomegaly, and jaundice

Investigations
- CBC (leukocytosis, anemia), LFTs (elevated ALP and hypoalbuminemia common; elevated transaminases and bilirubin variable), blood cultures, INR/PTT, stool cultures, and serology (*E. histolytica* and *Echinococcus*)
- CT or U/S are the imaging modalities used for diagnosis with abscess drainage for C&S to confirm diagnosis; MRI can also be used.

Treatment
- treat underlying cause
- pyogenic abscesses generally treated with antibiotic therapy (e.g. ceftriaxone and metronidazole or piperacillin-tazobactam) and U/S- or CT-guided percutaneous drainage or surgical drainage
- consider potential source of sepsis (e.g. biliary source, infected tumour)

Prognosis
- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition, elderly, ICU admissions, shock, cancer, cirrhosis, chronic kidney disease (CKD), acute respiratory failure, and biliary origin of abscess

Differential Diagnosis of Metastatic Liver Mass

Some **GU** **C**ancers **P**roduce **B**umpy **L**umps

Stomach
Genito**U**rinary cancers (kidney, ovary, uterus)
Colon
Pancreas
Breast
Lung

Neoplasms

BENIGN LIVER NEOPLASMS

Hemangioma (cavernous)
- pathogenesis: most common benign hepatic tumour; results from malformation and proliferation of vascular endothelial cells
- risk factors: M:F=3:1
- clinical features
  - usually small and asymptomatic, those greater than 10 cm are considered giant and may cause abdominal pain or discomfort
  - consumptive coagulopathy if giant (in children)
- investigations
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement on arterial phase with centripetal filling on delayed phases), U/S (homogeneous hyperechoic mass), MRI
  - avoid biopsy: may result in hemorrhage

- treatment
  - none if asymptomatic
  - in symptomatic patients or those with hemangiomas large enough causing mass effect, surgical resection should be considered after other causes of pain are excluded
  - surgical resection options: liver resection, hepatic artery ligation, enucleation, and in severe cases liver transplantation.
  - non-surgical treatment: hepatic artery embolization and radiotherapy

Focal Nodular Hyperplasia

- pathogenesis: unclear, hyperplastic response to vascular anomaly leading to disorganized growth of hepatocytes and bile ducts
- risk factors: female, reproductive age
- clinical features: usually asymptomatic, rarely grows or bleeds, and no malignant potential
- investigations: central stellate scar surrounded by homogenous lesion on CT scan; MRI, biopsy may be required
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential)
  - if confirmed to be FNH → no treatment required

Adenoma

- pathogenesis: benign abnormal growth of glandular epithelium
- risk factors: female, ages 20-50, estrogen (OCP, pregnancy), obesity, anabolic androgen use, and type 1 glycogen storage disease
- clinical features: asymptomatic, 25% present with RUQ pain or mass, may present with bleeding
- investigations: CT (well-demarcated masses, often heterogeneous enhancement on arterial phase, isodense on venous phase without washout of contrast), U/S, MRI, biopsy can be considered, with bleeding risk taken into account
- treatment
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to HCC and spontaneous rupture/hemorrhage

MALIGNANT LIVER NEOPLASMS

Primary

- most commonly HCC and cholangiocarcinoma
- others include angiosarcoma, hepatoblastoma, and hemangioendothelioma
- risk factors
  - chronic liver inflammation: cirrhosis from any cause, chronic hepatitis B (inherently oncogenic) and hepatitis C, hemochromatosis, α1-antitrypsin deficiency, and non-alcoholic steatohepatitis
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, betel nuts chewing
  - chemical carcinogens: aflatoxin, microcystin, and vinyl chloride (associated with angiosarcoma)
- clinical features
  - RUQ discomfort and right shoulder pain
  - jaundice, weakness, weight loss, and ± fever (if central tumour necrosis)
  - hepatomegaly, bruit, and hepatic friction rub
  - ascites with blood (sudden intra-abdominal hemorrhage)
  - paraneoplastic syndromes: hypoglycemia, hypercalcemia, erythrocytosis, and watery diarrhea
  - metastasis: lung, intra-abdominal lymph nodes, bone, adrenal gland, brain, and peritoneal seeding
- investigations
  - INR and LFTs: AST, ALT, ALP, bilirubin, and albumin
  - elevated ALP, bilirubin, and α-fetoprotein (80% of patients)
  - U/S (poorly-defined margins with internal echoes), triphasic CT (enhancement on arterial phase and washout on portal venous phase), and MRI
- treatment
  - cirrhosis is a relative contraindication to tumour resection due to decreased hepatic reserve
  - surgical: resection (10% of patients have resectable tumours)
  - liver transplant; may use bridging therapy while awaiting transplant
    - absolute contraindications: extrahepatic disease and vascular invasion
    - relative contraindications: dependent on liver transplant protocol based on staging criteria followed by transplant centre
  - non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), chemotherapy (consider sorafenib for HCC; preoperative chemotherapy for hepatoblastoma is standard of care), and radiotherapy
- prognosis
  - 5 yr survival: 18% of all patients; 40-70% of patients undergoing complete resection

Liver Transplantation Criteria for Hepatocellular Carcinoma

Milan Criteria*	1 tumour ≤5 cm Up to 3 tumours each ≤3 cm
UCSF Criteria*	1 tumour ≤6.5 cm Up to 3 tumours each ≤4.5 cm, total diameter ≤8 cm
Toronto Criteria*	No tumour size or number restrictions No systemic symptoms Not poorly differentiated

*Each criteria assumes no extrahepatic and no macrovascular invasion

Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, including Postoperatively)

	1 Point	2 Points	3 Points
Albumin (g/L)	>35	28-35	<28
Ascites	Absent	Easily controlled	Poorly controlled
Bilirubin (μmol/L)	<34	34-51	>51
(mg/dL)	<2.0	2.0-3.0	>3.0
Coagulation (INR)	<1.7	1.7-2.3	>2.3
Hepatic Encephalopathy	None	Minimal	
(Grade I-II)	Advanced		
(Grade III-IV)			

Points	Class	One Yr Survival	Two Yr Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Secondary

- metastases to the liver are the most common malignant tumours found in the liver
- etiology
  - GI (colorectal most common), lung, breast, pancreas, GI NET, stomach, melanoma, ovary, uterus, kidney, gallbladder, and prostate
- treatment
  - depends on the primary cancer site and prognosis
    - often liver metastases are a manifestation of Stage IV disease and chemotherapy is indicated
  - metastasectomy may be appropriate for cancers either through surgical resection or local treatment (i.e. embolization)
    - hepatic resection of metastatic colorectal liver metastases is standard of care as part of multi-modality treatment that includes chemotherapy if complete resection of the primary cancer and metastases is possible
    - transplant also a new and emerging alternative for metastatic disease in the liver
- prognosis
  - following liver resection for colorectal metastases is an overall survival of 30-60% at 5 yr

Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrahepatic cancers. They commonly arise from colorectal, lung, and breast cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure

Liver Transplantation

Table 26. Conditions Leading to Transplantation

Parenchymal Disease	Cholestatic Disease	Inborn Errors	Tumours
Chronic hepatitis B or C*	Biliary atresia**	α1-antitrypsin deficiency	Hepatocellular carcinoma
Alcoholic cirrhosis	Primary biliary cirrhosis	Wilson's disease	Hepatoblastoma
Acute liver failure	Sclerosing cholangitis	Hemochromatosis	Metastatic NETs
Budd-Chiari syndrome			Colorectal cancer
Congenital hepatic fibrosis			
CF			
Autoimmune hepatitis			
Cryptogenic cirrhosis			
Drug induced hepatotoxicity			
Non-alcoholic steatohepatitis			

*leading cause in adults; **leading cause in children

Living Liver Donors vs. Deceased Liver Donors
The right lobe of a living donor liver is transplanted into the recipient. This is due to the larger right lobe providing a greater graft volume to sustain the metabolic demand of recipients. Donor safety and graft suitability for recipients should be considered in living donor liver transplants. Whole livers from deceased donors are transplanted orthotopically into the recipient

Clinical Indications

- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially:
  - decompensated cirrhosis (ascites, esophageal variceal hemorrhage, spontaneous hepatic encephalopathy, coagulopathy, progressive jaundice, severe fatigue)
  - unresectable primary liver cancers
  - unresectable but localized liver metastasis of colorectal cancer - new emerging indication
  - acute liver failure
  - liver-based metabolic conditions including α-1-antitrypsin deficiency
- end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate
  - suitable HCC not amenable to liver resection

Criteria for Transplantation

- Model for End-Stage Liver Disease (MELD): prognostic model to estimate 3 mo survival following transjugular intrahepatic portosystemic shunt (TIPS) procedure and to prioritize patients awaiting liver transplant; based on creatinine, bilirubin, INR, sodium (MELD-Na), female sex, and serum albumin; MELD scores used to prioritize liver allocation
- Child-Turcotte-Pugh Score: classification system to assess the prognosis and the abdominal surgery perioperative mortality of chronic liver disease and cirrhosis; patient must have ≥7 points (Class B) for transplant evaluation

Contraindications

- active alcohol/substance use
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease
- active uncontrolled infection

Postoperative Complications

- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: HTN, renal disease, DM, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

Prognosis

- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

Biliary Tract

Cholelithiasis

Definition
- the presence of stones in the gallbladder

Pathogenesis
- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excess hepatic cholesterol secretion relative to bile salts and lecithin → supersaturated cholesterol which precipitates as gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors
- cholesterol stones
  - obesity
  - increasing age
  - prevalence higher in females (especially females <50 yr)
  - estrogens: female, multiparity, OCPs
  - impaired gallbladder emptying: starvation, TPN, DM
  - rapid weight loss: rapid cholesterol mobilization and biliary stasis
- pigment stones (contain calcium bilirubinate)
  - cirrhosis
  - chronic hemolysis
  - biliary stasis (strictures, dilation, biliary infection)
  - terminal ileal resection or disease (e.g. Crohn's disease)
- protective factors
  - statins, physical activity, vitamin C, poly- and monounsaturated fats and nuts, coffee

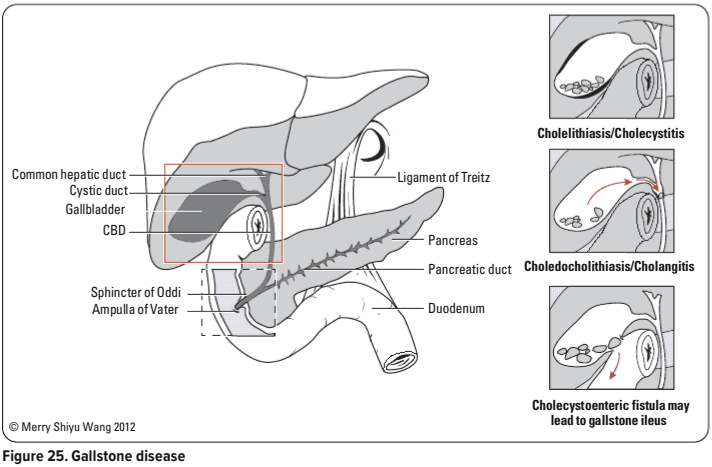


Figure 25. Gallstone disease

Clinical Features
- asymptomatic (80%): found incidentally
  - 18% risk of progression to symptomatic gallstone disease within 20 yr
  - most do NOT require treatment
  - consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli's disease, porcelain or calcified gallbladder), sickle cell disease, paediatric patient, bariatric surgery, or immunosuppression
- biliary colic (10-25%)

Investigations
- normal bloodwork: CBC, electrolytes, Cr, LFTs, bilirubin, lipase
- U/S: diagnostic procedure of choice
  - image for signs of inflammation, obstruction, and localization of stones
  - 95% specific for detecting stones

Risk Factors for Cholesterol Stones

4Fs
Fat
Female
Fertile
Forties

Summary of Biliary Tract Conditions

Gallbladder	Asymptomatic	Pain Only	Infection + Pain
Cholelithiasis	✓ (majority)		
Biliary Colic		✓	
Cholecystitis			✓
Common Bile Duct	**Asymptomatic**	**Pain Only**	**Infection + Pain**
Choledocholithiasis	✓ (majority)	✓	
Cholangitis			✓ (majority)

Biliary Colic

Pathogenesis
- gallstone transiently impacted in cystic duct, no infection

Clinical Features
- an episode of steady, severe dull pain in the epigastrium or RUQ lasting minutes to hours (<6 h), crescendo-decrescendo pattern
- can present with chest pain, right shoulder tip pain, scapular pain
- N/V
- frequently occurs at night or after fatty meal, not after fasting
- no peritoneal findings, no systemic signs

Investigations
- normal blood work: CBC, electrolytes, Cr, LFTs, bilirubin, lipase
- U/S shows cholelithiasis, may show stone in cystic duct (neck of gallbladder)

Treatment
- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success)
  - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, and vessel injury leading to liver damage
  - laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery

Acute Cholecystitis

Pathogenesis
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see *Acalculous Cholecystitis, GS57*)

Clinical Features
- often have history of biliary colic
- severe constant (>6 h) epigastric or RUQ pain, anorexia, N/V, and low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable and tender gallbladder (in 33%)
- Boas' sign: right subscapular pain

Investigations
- blood work: elevated WBC and left shift, mildly elevated bilirubin concerning for bile duct obstruction (either stones or Mirizzi syndrome)
- U/S: 98% sensitive, consider HIDA scan if U/S negative
  - signs: gallbladder wall thickening >4 mm, edema (double-wall sign), gallbladder sludge, cholelithiasis, pericholecystic fluid, and sonographic Murphy's sign

Complications
- gangrenous gallbladder (20%) most common complication
- perforation (10%): result in abscess formation or rarely local peritonitis
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct
- empyema of gallbladder: suppurative cholecystitis (pus in gallbladder) and sick patient
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall, or pericholecystic space (risk in diabetic patient); organisms involved in secondary infection: *C. welchii, E. coli, Klebsiella*, anaerobic streptococci, Enterococcus
- cholecystoenteric fistula (from repeated attacks of cholecystitis) can lead to gallstone ileus

Treatment
- admit, hydrate, NPO, NG tube (if persistent vomiting from associated ileus), analgesics
- antibiotics
  - cefazolin if uncomplicated cholecystitis
- ERCP prior to surgery if CBD stones are present on U/S
  - MRCP ± ERCP if CBD is markedly dilated or CBD stones suspected
- cholecystectomy
  - early (within 72 h) vs. delayed (after 6 wk, not standard)
  - equal morbidity and mortality
  - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
  - emergent OR indicated if high-risk, e.g. sepsis
  - laparoscopic is standard of care (convert to open for complications or difficult case)
    - reduced risk of wound infections, shorter hospital stay, reduced postoperative pain, and increased risk of bile duct injury
- intraoperative cholangiography (IOC)
  - indications: clarify bile duct anatomy, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), and jaundice
  - has been mostly replaced by preoperative MRCP

Biliary colic is a pain that comes and goes, but cholecystitis is a pain which is constant and usually increasing

2 Most Important Lab Tests for Biliary Pain

Lipase: to determine if element of pancreatitis

Bilirubin: to determine if bile duct obstruction

Biliary colic is treated with analgesia and elective cholecystectomy
Acute cholecystitis is treated with antibiotics and early cholecystectomy if surgical risk appropriate

Toronto Video Atlas of Surgery: Standard Laparoscopic Cholecystectomy
TVAsurg is an open access library of animation enhanced surgical videos created by surgeons in Toronto. For a video simulation of a standard laparoscopic cholecystectomy, see http://pie.med.utoronto.ca/TVASurg/project/standardlapchole/

Mirizzi Syndrome
Extrinsic compression of the CHD by a gallstone in the cystic duct or Hartmann's pouch. Impacted gallstone may erode into the CHD or CBD, creating a cholecystohepatic or cholecystocholedochal fistula; Mirizzi syndrome has an association with gallbladder cancer

Rouviere's Sulcus
Fissure between right lobe and caudate process (segment I) of liver; keeping dissection anterior to this landmark can minimize bile duct injury

Critical View of Safety (CVS)
Decreases risk of injury to CBD during laparoscopic cholecystectomy, 3 criteria are required to achieve the CVS:
1. The hepatocystic triangle (formed by the cystic duct, CHD, and inferior edge of the liver) is cleared of fat and fibrous tissue
2. The lower one third of the gallbladder is separated from the liver to expose the cystic plate
3. Two and only two structures should be seen entering the gallbladder (cystic duct and artery)

- percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated
- some centres can perform percutaneous stone extraction to avoid cholecystectomy or create fistulas from stomach to gallbladder to decompress and create an internal cholecystostomy tube without the morbidity of percutaneous tube

Early vs. Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis: A Meta-Analysis of Randomized Clinical Trials
Am J Surg 2008;196(1):40-47
Purpose: Evaluate effects of early versus late laparoscopic cholecystectomy in treatment of acute cholecystitis.
Methods: Systematic review and meta-analysis of randomized studies in Medline, Embase, Cochrane, and Google Scholar between 1987-2006. Endpoints included rates of conversion to open surgery, postoperative complications, length of stay, and duration of surgery.
Results: 4 RCTs included with a total of 375 patients. No differences were found between early and late groups in rates of conversion to open surgery (P=0.718) or postoperative complications (P=0.813). Length of stay was shorter for the early group (P= 0.0005) while duration of surgery was shorter for the late group (P=0.002).
Conclusions: Early laparoscopic cholecystectomy for acute cholecystitis reduces length of hospital stay with comparable rates of conversion to open surgery and postoperative complications compared with late surgery.

Acalculous Cholecystitis

Definition
- acute or chronic cholecystitis in the absence of stones

Pathogenesis
- typically due to gallbladder ischemia and stasis

Risk Factors
- ICU admission (most common), DM, immunosuppression, trauma patient, TPN, and sepsis

Clinical Features
- see *Acute Cholecystitis, GS56*
- occurs in 10% of cases of acute cholecystitis

Investigations
- bloodwork: CBC, electrolytes, Cr, LFTs, liver enzymes, bilirubin, and lipase
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis, GS56*)
- CT or HIDA scan

Treatment
- NPO, IV fluids, and pain management
- IV broad-spectrum antibiotics, cholecystectomy
- if patient unstable → percutaneous cholecystostomy

Choledocholithiasis

Definition
- stones in CBD

Clinical Features
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, and fluctuating jaundice
- primary vs. secondary stones
  - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, and CF)
  - secondary: formed in gallbladder (85% of cases in the U.S.)

American Society of Gastrointestinal Endoscopy 2019 Guideline on Role of Endoscopy in Evaluating Choledocolithiasis

Proceed directly to ERCP
- CBD stone on U/S
- Clinical ascending cholangitis
- Bilirubin >4 mg/dL (>347 umol/L) & dilated CBD on U/S

Perform U/S, MRCP, Laparoscopic IOC or Intraoperative US
- Abnormal liver tests
- Age >55 yr
- Dilated CBD on U/S

Investigations
- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GGT later
- lipase: to rule out gallstone pancreatitis
- U/S: intra-/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
- MRCP (90% sensitive)
  - visualization of ampullary region, biliary, and pancreatic anatomy
  - non-invasive diagnostic test of choice
- ERCP
  - CBD stones in periampullary region
  - diagnostic and therapeutic; removal of stones and sphincterotomy possible
  - complications: retained stones, ERCP pancreatitis (1-2%), pancreatic or biliary sepsis
- Percutaneous Transhepatic Cholangiography
  - percutaneous approach to the proximal biliary tree (i.e. intrahepatic biliary system) via the hepatic parenchyma
  - useful for proximal bile duct obstruction or when ERCP fails or not available
  - contraindications: ascites, peri/intrahepatic sepsis, and disease of right lower lung or pleura
  - complications: bile peritonitis, chylothorax, pneumothorax, biliary sepsis, and hemobilia
- Intraoperative Cholangiography (IOC)
  - intraoperative injection of radiographic contrast into the cystic duct to evaluate CBD during laparoscopic cholecystectomy
  - useful for identifying CBD stones, clarifying biliary anatomy, and preventing CBD injury during cholecystectomy

Complications
- cholangitis, pancreatitis, biliary stricture, and biliary cirrhosis

Treatment
- treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients
- biliary tree flushing with laparoscopic cholecystectomy:
  - during a laparoscopic cholecystectomy ± cholangiogram, the cystic duct can be flushed to the CBD with the use of glucagon to relax the sphincter between the CBD and duodenum. Can also use cholangiogram to confirm stones flushed into duodenum

Acute Cholangitis

Pathogenesis
- obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration, and biliary sepsis – may be life-threatening, especially in elderly

Etiology
- choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), and biliary stent
- organisms: *E. coli, Klebsiella, Enterobacter, Pseudomonas, Enterococcus, B. fragilis*, and *Proteus*

Clinical Features
- Charcot's triad: fever, RUQ pain, and jaundice
- Reynold's pentad: Charcot's triad, hypotension, and altered mental status
- may have N/V, abdominal distention, ileus, acholic stools, and tea-coloured urine (elevated direct bilirubin)

Charcot's Triad
Fever, RUQ pain, jaundice

Reynolds' Pentad
Fever, RUQ pain, jaundice, shock, and altered mental status

Investigations
- CBC: elevated WBC + left shift
- may have positive blood cultures
- LFTs: obstructive picture (elevated ALP, GGT, and conjugated bilirubin, possible mild increase in AST, ALT)
- lipase: rule out pancreatitis
- U/S: intra-/extra-hepatic duct dilatation
- CT: bile duct dilatation and can identify biliary stenosis
- MRCP when diagnosis is unclear

Common Bacteria in Biliary Tract

KEEPS
K*lebsiella*
E*nterococcus*
E*. coli, Enterobacter*
P*roteus, Pseudomonas*
S*erratia*

Treatment
- initial: NPO, fluid and electrolyte resuscitation, ± NG tube, IV antibiotics (treats 80%)
- biliary decompression
  - ERCP + sphincterotomy: diagnostic and therapeutic
  - PTC with catheter drainage: if ERCP not available or unsuccessful
  - open or laparoscopic CBD exploration and T-tube placement if above fails
- in addition to biliary decompression, the underlying cause should be addressed. In the case of patients with choledocholithiasis, elective cholecystectomy is recommended after resolution of acute cholangitis to prevent re-occurrence

Prognosis
- suppurative cholangitis mortality rate: 20-30%

Gallstone Ileus

Pathogenesis
- repeated inflammation causes a cholecystoenteric fistula (usually duodenal) → large gallstone enters the GI tract (impacting near the ileocecal valve) causing a mechanical bowel obstruction (note: ileus is a misnomer in this context)

Rigler's Triad of Gallstone Ileus
Pneumobilia
Small bowel obstruction
Gallstone

Clinical Features
- crampy abdominal pain, N/V, constipation/obstipation (see *Large Bowel Obstruction, GS37*)

Investigations
- AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, and air in biliary tree (pneumobilia) (40%)
- CT: biliary tract air, obstruction, and gallstone in intestine
- Rigler's triad: pneumobilia, SBO (partial or complete), and gallstone (usually in right iliac fossa)

Bouveret's Syndrome
Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula

Treatment
- fluid resuscitation, NG tube decompression
- surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- may close fistula surgically or manage expectantly (can resolve spontaneously)
- cholecystectomy is generally not performed

Carcinoma of the Gallbladder

Risk Factors
- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (Salmonella, Helicobacter), primary sclerosing cholangitis, and abnormal pancreaticobiliary duct junction

Clinical Features
- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of open cholecystectomies OR 0.1% in laparoscopic cholecystectomies)
- many patients are asymptomatic until late
- local: non-specific RUQ pain ± palpable RUQ mass
- Courvoisier's gallbladder sign: enlarged gallbladder and painless jaundice due to obstruction of CBD, suggestive of gallbladder or pancreatic malignancy
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, anorexia, N/V, weight loss, and malaise
- early local extension to liver, peritoneum, may extend to stomach, duodenum
- early metastasis common to lung, pleura, liver, bone

Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, and fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as, polyps, staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, and distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

Treatment
- if carcinoma of the gallbladder is suspected preoperatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, and dissection of hepatoduodenal lymph nodes

Prognosis
- poor 5 yr survival (20%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

Cholangiocarcinoma

Definition
- malignancy of the epithelial cells of extra- or intrahepatic bile ducts

Risk Factors
- ages 50-70, gallstones, UC, primary sclerosing cholangitis, choledochal cyst, Clonorchis sinensis infection (liver fluke), chronic intrahepatic stones (hepatolithiasis), genetic disorders (Lynch syndrome, CF, multiple biliary papillomatosis, BAP1 tumour predisposition syndrome)

Clinical Features
- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, and pale stools
- anorexia, weight loss, RUQ pain, Courvoisier's sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery, peritoneum, lungs, pleura, liver
- Klatskin tumour: cholangiocarcinoma located at bifurcation of CHD

Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma

Investigations
- LFTs show obstructive picture, carbohydrate antigen 19-9 (CA 19-9), CEA may be elevated
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

Treatment
- if resectable: biliary drainage and wide excision margin
- intrahepatic lesions: liver resection after clear discussion at multidisciplinary tumour boards and prognosis understood
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure

- unresectable lesions: stent or choledochojejunostomy (surgical bypass)
- chemotherapy ± radiotherapy
- role for transplantation in select patients with Klatskin tumours or NET with no evidence of extrahepatic disease and relative stability

Prognosis
- overall 5 yr survival: localized 30%, regional 24%, distant 2%

Pancreas

Acute Pancreatitis

- see Gastroenterology, G48

GALLSTONE PANCREATITIS (45% of Acute Pancreatitis)

Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (Pancreatitis of Any Etiology)
- pain (epigastric pain radiating to back), N/V, ileus, peritoneal signs, jaundice, and fever
- Inglefinger's sign: pain worse when supine, and better when sitting forward
- may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)
  - APACHE II score for determining prognosis of severe acute pancreatitis
- physical exam may show tachypnea, tachycardia, hypotension, abdominal distention and tenderness, Cullen's sign, and Grey Turner's sign

Investigations
- lipase (most sensitive and specific), elevated amylase (higher than alcoholic pancreatitis), and leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), and edematous pancreas
- CXR, AXR, and CT (if severe to evaluate for complications)

Treatment
- supportive: e.g. NPO, hydration, analgesia, and early enteral nutrition
- antibiotics are not indicated for initial diagnosis. This is reserved for clear signs of infection on imaging
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if CBD stone impacted or cholangitis
- surgical indications in acute pancreatitis (rare):
  - drain placement and debridement for necrotizing pancreatitis if refractory to medical management, if septic, or in ICU without other sources of sepsis

Complications
- local complications
  - acute fluid collections
  - walled-off pancreatic fluid collection/pseudocyst (>4 wk)
  - abscess/infection, necrosis
- systemic complications
  - splenic/mesenteric/portal vessel thrombosis
  - pancreatic ascites/pancreatic pleural effusion
  - DM (due to pancreatic & insulin insufficiency)
  - ARDS/sepsis/multiorgan failure
  - coagulopathy/DIC
  - severe hypocalcemia

Ranson's Criteria
A. At admission
1. Ages >55 yr
2. WBC >16 x 10^9/L
3. Glucose >11 mmol/L
4. LDH ≥350 IU/L
5. AST >250 IU/L

B. During initial 48 h
1. Hct drop >10%
2. BUN rise >1.8 mmol/L
3. Arterial PO_2 <60 mmHg
4. Base deficit >4 mmol/L
5. Calcium <2 mmol/L
6. Fluid sequestration >6 L

C. Interpretation
<3 = severe pancreatitis unlikely (2% mortality)
≥3 = high mortality (≥15%)

Chronic Pancreatitis

- see Gastroenterology, G50

Surgical Treatment
- treatment is generally medical
- indications for surgery
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, and rupture
  - CBD obstruction (e.g. strictures) and duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- preoperative CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery
- surgical options
  - drainage procedures: only effective if ductal system is dilated
  - Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
  - pancreatectomy: best option in absence of dilated duct
  - Whipple procedure (pancreaticoduodenectomy): proximal disease
  - distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy: distal disease
  - total pancreatectomy: refractory disease
- islet cells autotransplantation can be used to control insulin-related morbidity
  - denervation of celiac ganglion and splanchnic nerves

WALLED-OFF PANCREATIC FLUID COLLECTIONS (PSEUDOCYSTS)
- localized fluid collections rich in pancreatic enzymes, with a non-epithelialized wall consisting of fibrous and granulation tissue
- complication of chronic and/or acute pancreatitis
- up to 40% resolve spontaneously
- cyst wall must be mature prior to drainage (4-6 wk)
- pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first

Pseudocyst Management
- if asymptomatic: expectant management
- if symptomatic: choice of drainage procedure depends on location of fluid collection
  - endoscopic drainage: transmural vs. transpapillary (pseudoaneurysm an absolute contraindication, must embolize first)
  - surgical drainage: cystogastrostomy vs. cystoduodenostomy vs. cystojejunostomy
  - percutaneous catheter drainage
  - resection
  - if draining, attempt to biopsy cyst wall to rule out cystadenocarcinoma

The hallmark of chronic pancreatitis is epigastric pain radiating to the back

Total Pancreatectomy and Islet Autotransplantation: A Decade Nationwide Analysis
World J Transplant 2016;6(1):233-238
Purpose: To investigate outcomes and predictors of in-hospital morbidity and mortality after total pancreatectomy (TP) and islet autotransplantation.
Results: A total of 923 patients underwent IAT after pancreatectomy during 2002-2012. The most common indication of surgery was chronic pancreatitis (86%) followed by acute pancreatitis (12%). Overall mortality and morbidity of patients were 0% and 57.8 %, respectively. Postoperative hypoinsulinemia was reported in 42.3% of patients, indicating that 57.7% of patients were insulin independent during hospitalization. Predictors of in-hospital morbidity were obesity, fluid and electrolyte disorders, alcohol use, and weight loss.
Conclusion: Total pancreatectomy + islet autotransplantation is a safe procedure with no mortality, acceptable morbidity, and achieved high rate of early insulin independence. Obesity is the most significant predictor of in-hospital morbidity.

Pancreatic Cancer

Epidemiology
- 4th most common cause of cancer-related mortality in both men and women in Canada
- M:F=1.3:1, average ages: 50-70

Risk Factors
- increased age
- smoking: 2-5x increased risk, most clearly established risk factor
- high fat/low fibre diets
- heavy alcohol use
- obesity
- DM, chronic pancreatitis
- partial gastrectomy
- cholecystectomy
- chemicals: β-naphthylamine, benzidine
- African descent

Clinical Features
- the most common presenting symptoms are abdominal pain, jaundice, and weight loss
- head of the pancreas (70%)
  - pancreatic head tumours typically present with jaundice, steatorrhea, and weight loss
  - other features include anorexia, dark urine, hepatomegaly, cachexia, Courvoisier's sign, recent onset DM
- body or tail of pancreas (30%)
  - tends to present later and usually inoperable (80% are unresectable at diagnosis)
  - weight loss, vague mid-epigastric pain
  - <10% jaundiced

Investigations
- serum chemistry is non-specific, LFTs may show obstructive jaundice (elevated ALP and bilirubin)
- CA 19-9 most useful serum marker of pancreatic cancer
- U/S, CT (also evaluates metastasis and resectability) ± ERCP, MRI, EUS

Pathology
- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: pancreatic NETs (non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma), mucinous cystic neoplasm (MCN), acinar cell carcinoma
- see *Surgical Endocrinology, GS72* for functional pancreatic NETs

Treatment
- resectable (10-20% of pancreatic cancer)
  - no involvement of liver, peritoneum, or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure <5% mortality
  - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
  - adjuvant chemotherapy recommended (gemcitabine ± capecitabine, 5-FU/leucovorin)
- locally advanced, borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
- locally advanced, non-resectable (palliative → relieve pain, obstruction)
  - encasement of major vascular structures including arteries
  - most body/tail tumours are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
  - palliative chemotherapy (gemcitabine + nab-paclitaxel, FOLFIRINOX) ± radiotherapy

Prognosis
- most important poor prognostic indicators are lymph node status, margin status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5 yr survival for all patients with pancreas cancer is 1%; following surgical resection 5 yr survival is 20%
- median survival for unresectable disease: 3-6 mo if metastatic, 8-12 mo if locally advanced at presentation

Table 27. TNM Classification System for Exocrine Tumours of the Pancreas (AJCC 8th edition)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma *in situ*	N1	Metastasis in one to three regional lymph nodes		
T1	Tumour ≤2 cm in greatest dimension				
N2	Metastasis in four or more regional lymph nodes				
T2	Tumour >2 cm and ≤4 cm in greatest dimension				
T3	Tumour >4 cm in greatest dimension				
T4	Tumour involves celiac axis, SMA, or common hepatic artery				

Trousseau's Sign
Spontaneous peripheral venous thrombosis, often associated with pancreatic and other cancers

Vague abdominal pain with weight loss ± jaundice in a patient over 50 yr is pancreatic cancer until proven otherwise

Courvoisier's Sign
Palpable, nontender, distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger

Steps of a Whipple Resection (Pancreaticoduodenectomy)
1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the hepatic flexure of the colon
3. Mobilization of the duodenum (Kocher maneuver) and head of the pancreas
4. Identification of the superior mesenteric vein and mobilization of the pancreatic neck
5. Mobilization of the stomach; dissection of the hepatoduodenal ligament and cholecystectomy
6. Division of the stomach, proximal jejunum, and CBD
7. Transection of the pancreatic neck and dissection of the uncinate process from the retroperitoneum
8. Restoration of gastrointestinal continuity: construction of a pancreaticojejunostomy, hepaticojejunostomy, gastrojejunostomy using a neoduodenum

Remove
- CBD
- Gallbladder
- Duodenum
- Pancreatic head
- Distal stomach (sometimes)

Oncological Benefits of Neoadjuvant Chemoradiation with Gemcitabine vs. Upfront Surgery in Patients with Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial
Ann Surg 2018;268:215-222
Purpose: To determine whether neoadjuvant treatment increases survival in patients with borderline resectable pancreatic cancer (BRPC).
Methods: A total of 50 patients were randomized to neoadjuvant gemcitabine-based chemoradiotherapy or upfront surgery.
Results: The 2-yr survival rate (2YSR) and median survival of patients treated with neoadjuvant chemoradiation was significantly improved (40.7% 2YSR, 21 mo median survival) compared to upfront surgery (26.1% 2YSR, 12 mo median survival). The R0 resection rate was also significantly increased in the neoadjuvant chemoradiation group.
Conclusion: Neoadjuvant chemoradiation provides survival and surgical benefits in patients with BRPC.

Table 28. Staging and Treatment of Pancreatic Cancer

Stage	Classification	5 Yr Survival	Treatment
0	Tis, N0, M0		Surgical resection ± chemotherapy
IA	T1, N0, M0	14%	Same as above
IB	T2, N0, M0	12%	Same as above
IIA	T3, N0, M0	7%	Same as above
IIB	T1-3, N1, M0	5%	Same as above
III	T1-3, N2, M0 T4, any N, M0	3%	Borderline resectable, trial of chemotherapy and radiation
IV	any T, any N, M1	1%	Non-resectable, palliative treatments

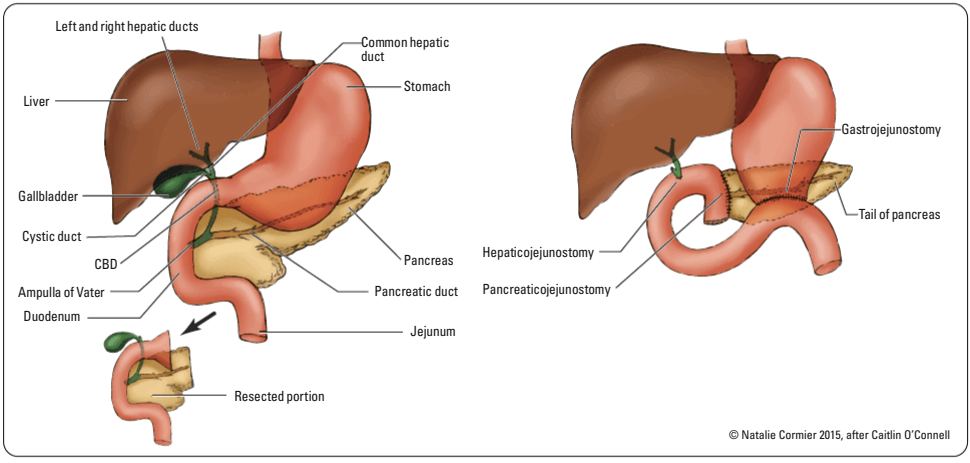


Figure 26. Schematic of Whipple resection showing the resected components

Spleen

Splenic Trauma

Clinical Features

- most common intra-abdominal organ injury in blunt trauma (especially can occur in people with splenomegaly)
- may have Kehr's sign
- patients may be hemodynamically unstable with altered mental status
- initial presentation may be masked by other injuries and contained ruptures may have few symptoms

Kehr's Sign
Left shoulder pain due to diaphragmatic irritation from splenic rupture, worsens with inspiration

Investigations

- FAST (used in trauma with hemodynamically unstable patients)
- CT with oral or IV contrast (once stable or when FAST negative)

Treatment

- non-operative
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative
  - hemodynamically unstable patients with positive FAST will undergo emergent operative surgical exploration
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh (if patient is hemodynamically stable)
  - splenectomy if patient unstable or high-grade injury or ongoing bleeding with hemodynamic instability
  - packing the spleen with temporary abdominal closure and relook laparotomy in 48 h

Splenectomy

Indications
- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenic purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenic purpura (TTP), and sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIG

Indication of Splenectomy

SHIRTS
Splenic abscess/splenomegaly
Hereditary spherocytosis
Immune thrombocytopenic purpura
Rupture of spleen
Thrombotic thrombocytopenic purpura
Splenic vein thrombosis

Complications
- short-term
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas) and their vascular supply
  - postoperative thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk <16 yr)
  - splenosis: intra-abdominal "seeding" of splenic tissue during removal
  - increased risk of malignancy, DVT, and PE
- 50% mortality

Prophylaxis
- vaccinations, ideally 2 wk pre- or postoperative (pneumococcal, *H. influenzae*, and meningococcus)
- liberal use of penicillin especially in children <6 yr

Splenic Infarct

Pathophysiology
- splenic artery occlusion or oxygen-delivery insufficiency leading to parenchymal ischemia and necrosis
- can occur in sickle cell disease, thromboembolism, myelofibrosis, CML, and hypercoagulable states

Clinical Features
- patient can be asymptomatic or can have LUQ pain (70%), N/V, fever, chills, and Kehr's sign

Investigations
- CT with contrast; MRI
- peripheral blood smear abnormalities

Treatment
- non-operative: close follow-up, analgesia
- indications for splenectomy: complications such as rupture, abscess, persistent pseudocyst, bleeding, or sepsis

Breast

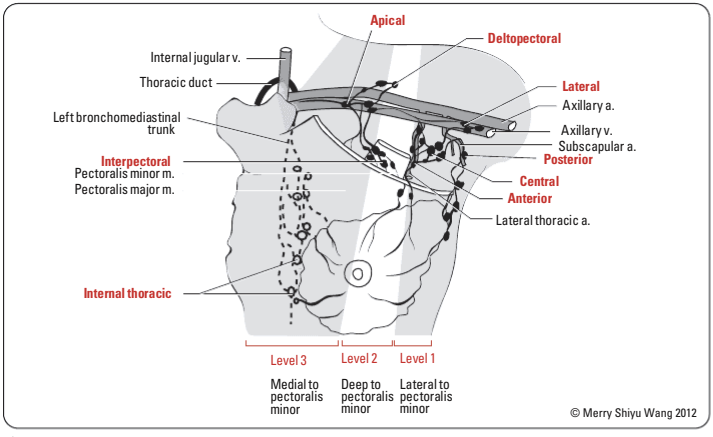


Figure 27. Anatomy of the breast

Levels of Axillary Lymph Nodes
Level I: lateral to pectoralis minor
Level II: deep to pectoralis minor
Level III: medial to pectoralis minor (higher level of nodal involvement = worse prognosis)

DDx for Breast Mass
Benign
- Fibrocystic changes
- Fibroepithelial lesions (fibroadenoma most common; benign phyllodes)
- Fat necrosis
- Papilloma/papillomatosis
- Galactocele
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
- Abscess
- Silicone implant

Malignant
- Breast cancer (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)

Benign Breast Lesions

Three Categories
1. non-proliferative
2. proliferative without atypia
3. atypical hyperplasia

NON-PROLIFERATIVE LESIONS
- benign breast condition characterized by fibrous and cystic changes in the breast (fibrocystic changes/disease)
- most common: breast cysts
- other lesions include papillary apocrine change, epithelial-related calcifications, and mild hyperplasia of the usual type
- no increased risk of breast cancer
- age 30 to menopause (and after if hormone replacement therapy (HRT) used)
- clinical features
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, and nipple discharge (straw-like, brown, or green)
- treatment
  - evaluation of breast mass (U/S, mammography as indicated) and reassurance
  - analgesia (e.g. ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

PROLIFERATIVE LESIONS – WITHOUT ATYPIA

Table 29. Proliferative Lesions - Without Atypia

		Clinical Features	Diagnosis	Treatment	Risk of Breast Cancer
Fibroadenoma	Most common breast tumour in women <30 yr	Nodules: firm, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone-dependent (unlike cysts), needle aspiration yields no fluid	Core or excisional biopsy sometimes required if concerned about malignancy U/S and FNA alone cannot differentiate fibroadenoma from phyllodes tumour	Generally conservative serial observation Consider excision if size 2-3 cm and growing on serial U/S (q6 mo x 2 yr is usual follow-up), if symptomatic, formed after age 35, patient preference or features on core biopsy suggestive of a phyllodes tumour	Increased if complex, adjacent atypia or strong family history of breast cancer
Intraductal Papilloma	Solitary intraductal benign polyp	Can present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge = pathologic nipple discharge), breast mass, nodule on U/S		Surgical excision of involved duct to ensure no atypia	Can harbour areas of atypia or DCIS
Usual Ductal Hyperplasia	Increased number of cells within the ductal space	Incidental finding on biopsy of mammographic abnormalities or breast masses		None required	Generally low-risk, slightly increased if moderate or florid hyperplasia
Sclerosing Adenosis	Lobular lesion with increased fibrous tissue and glandular cells	Mass or mammographic abnormality		None required	Low-risk

ATYPICAL HYPERPLASIA
- can involve ducts (atypical ductal hyperplasia) or lobules (atypical lobular hyperplasia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

OTHER LESIONS

Fat Necrosis
- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness, ± ecchymosis
- regress spontaneously, but complete imaging ± biopsy to rule out carcinoma
- oil cysts on mammography are pathognomonic for fat necrosis

Mammary Duct Ectasia
- obstruction of a subareolar duct (see Obstetrics, *Mastitis, OB48*)

Abscess
- lactational vs. non-lactational (periductal/subareolar) (see Obstetrics, *Mastitis, OB48*)

Breast Cancer

Epidemiology
- leading cancer diagnosis in women in North America, 2nd leading cause of cancer mortality in women
- 1 in 8 (12.9% lifetime risk) women in Canada will be diagnosed with breast cancer in their lifetime
- 1 in 31 women in Canada will die from breast cancer
- all age relative survival is 87%

Female sex, followed by age, are the two greatest risk factors for breast cancer

Risk Factors
- sex (99% female)
- age (83% >50 yr)
- personal history of breast cancer and/or prior breast biopsy (regardless of pathology)
- family history of breast cancer (greater risk if relative was first degree and premenopausal)
- estrogen exposure
  - nulliparity, first pregnancy >30 yr, menarche <12 yr, or menopause >55 yr
  - decreased risk with lactation, early menopause, and early childbirth
  - >5 yr HRT use, >10 yr OCP use
- high breast density
- radiation exposure (e.g. mantle radiation for Hodgkin's disease)
- BRCA1 and BRCA2 gene mutations
- alcohol use, obesity, and sedentary lifestyle

Any palpable dominant breast mass requires further investigation

Male Breast Cancer (<1%)
- most commonly invasive ductal carcinoma
- often diagnosed at later stages
- stage-for-stage similar prognosis to breast cancer in females
- consider genetic testing: most often hormone receptor positive

Breast Lymphatic Drainage:
Axillary lymph nodes
Internal mammary lymph nodes
Infra-/supra-clavicular lymph nodes

Investigations
- see margin for physical exam findings
- mammography
  - indications: screening guidelines (see Family Medicine, FM4)
  - findings indicative of higher risk of malignancy
    - mass that is poorly defined, spiculated border
    - microcalcifications
    - architectural distortion
    - interval mammographic changes
  - normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity. Use annual MRI and mammography for patients with 25% lifetime risk of breast cancer
  - Digital Breast Tomosynthesis (DBT): improved lesion localization and characterization in noncalcified lesions
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
  - metastatic workup indicated in Stage II-IV disease: bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), CT head (if specific neurological symptoms)

Physical Exam Findings in Breast Cancer:
Lump/mass: Often firm, irregular, non-mobile, unilateral
Pain: Usually thought of as painless, however pain may be present with rapidly expanding tumours or inflammatory cancer
Inflammation (and peau d'orange): There are many benign causes of inflammation, however inflammatory cancer can present similarly
Nipple or skin retractions/changes: Nipple or skin retractions/changes: Attachment of the tumour to skin/nipple may cause retraction/distortion
Nipple discharge: Majority due to benign causes, bloody spontaneous discharge should be investigated for malignancy

Diagnostic Procedures
- "triple test" for diagnosis of breast cancer:
  - clinical breast exam
  - imaging
    - ≥30 yr: mammography and U/S
    - <30 yr or lactating or pregnant: U/S (high breast density)
  - pathology (biopsy)
    - U/S or mammography guided core needle biopsy: most common
    - needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
    - excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

Genetic Screening
- consider testing for BRCA1/2 if:
  - young patient (<35 yr)
  - bilateral breast cancer in patients <50 yr
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer

Phyllodes tumours are rare fibroepithelial breast tumours that can be benign or malignant that mostly affect women from 35-55 yr

Staging
- patients are assigned a clinical stage preoperatively (cTNM); following surgery the pathologic stage is determined (pTNM)
- clinical
  - tumour size by palpation, mammogram, U/S, and/or MRI
  - nodal involvement by palpation, imaging
  - metastasis by physical exam, CXR, abdominal U/S (or CT chest/abdomen/pelvis), and bone scan (usually done postoperative if node-positive disease)
- pathological
  - tumour size and type
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear, and mitotic grade
  - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, and sentinel lymph node biopsy (SLNB) positive/negative
  - tumour biology: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu oncogene status
  - margins: for invasive breast cancer, negative margin is sufficient; for DCIS prefer 2 mm margin
  - lymphovascular invasion (LVI)
  - extensive *in situ* component (EIC): DCIS in surrounding tissue
  - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

Table 30. TNM Classification System for Staging of Breast Cancer (AJCC 2017)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	**NX**	Regional lymph nodes cannot be assessed	**M0**	No distant metastasis
T0	No evidence of primary tumour	**N0**	No regional lymph node metastasis	**M1**	Distant metastasis
Tis	Ductal carcinoma *in situ*	**N1**	Involvement of 1-3 axillary lymph nodes and/or clinically negative internal mammary nodes on sentinel node biopsy		
T1	Tumour ≤2 cm in greatest dimension				
N2	Involvement of 4-9 axillary lymph nodes or clinically positive ipsilateral internal mammary lymph node				
T2	Tumour >2 cm but ≤5 cm in greatest dimension				
T3	Tumour >5 cm in greatest dimension				
T4	Tumour of any size with direct extension to chest wall and/or skin				

Favourable Features	Unfavourable Features
<2 cm	>5 cm
Grade I (low grade)	Grade III (high grade)
Node negative	Node positive
ER positive	ER negative
Mucinous pattern	Inflammatory cancer
	Her2/Neu positive
	Positive margins
	Lymphovascularinvasion
	Epidermal inclusion cyst
	Dermal lymphatics involved

Pathology

NON-INVASIVE

Ductal Carcinoma *in situ* (DCIS)
- proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
- 80% non-palpable; detected by screening mammogram as microcalcifications
- risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
- treatment
  - lumpectomy with wide excision margins + radiation (5-10% risk of invasive cancer)
  - mastectomy if large area of disease, high grade, or multifocal (risk of invasive cancer reduced to 1%)
  - possibly tamoxifen as an adjuvant treatment
  - 99% 5 yr survival

Analysis of Circulating Tumour DNA to Monitor Metastatic Breast Cancer
NEJM 2013;368:1199-1209
Study: The quantification of circulating tumour DNA, cancer antigen 15-3 (CA 15-3), and circulating tumour cells in 30 women with metastatic breast cancer receiving systemic therapy. The results were compared with radiographic imaging of tumours.
Results/Conclusions: Circulating tumour DNA was detected in 97% of women and showed greater correlation with changes in tumour burden than did CA 15-3 or circulating tumour cells, providing the earliest measure of treatment response in 53% of women. CA 15-3 and circulating tumour cells were detected in 78% and 87% of women, respectively. Circulating tumour DNA may therefore be an informative biomarker for metastatic breast cancer.

Lobular Carcinoma *in situ* (LCIS)
- neoplastic cells completely contained within breast lobule
- no palpable mass and no mammographic findings; usually incidental finding on breast biopsy for another indication
- LCIS is a risk factor for invasive carcinoma (approximately 1%/yr)
- treatment
  - if diagnosed on core biopsy, excisional biopsy necessary to rule out malignancy
  - if diagnosed on excisional biopsy, wide excision not needed since LCIS is often multicentric and not managed as precursor lesion
  - clinical follow-up and surveillance; consider chemoprevention (e.g. tamoxifen)

10 Year Survival after Breast-Conserving Surgery Plus Radiotherapy Compared with Mastectomy in Early Breast Cancer in The Netherlands: A Population-Based Study
Lancet Oncol 2016;17(8):1158
See Landmark General and Thoracic Surgery Trials table for more information on the 10 yr survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer.

INVASIVE

Invasive Ductal Carcinoma (most common 80%)
- originates from ductal epithelium and infiltrates supporting stroma
- four types: tubular, mucinous, medullary, and inflammatory
- characteristics: hard, scirrhous, infiltrating tentacles, and gritty on cross-section
  - divided into three grades based on cytologic and architectural features: well differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3)

Invasive Lobular Carcinoma (8-10%)
- originates from lobular epithelium, 20% bilateral
- subtle thickening originating from lobes/lobules; usually positive for estrogen and progesterone receptors
- harder to detect on mammography due to lack of microcalcifications (may benefit from MRI)

Paget's Disease of the Breast (1-3%)
- ductal carcinoma that invades nipple with scaling, ulceration, erythema, and eczematous lesion

Inflammatory Carcinoma (1-3%)
- most aggressive form of breast cancer
- ductal carcinoma that grows in nests (vs. solid tumour); invades and blocks dermal lymphatics
- clinical features: erythema, skin edema, warm, swollen, and tender breast ± lump, nipple changes
- peau d'orange indicates advanced disease (IIIb-IV)

Sarcomas: rare
- most commonly phyllodes tumour, a variant of fibroadenoma with potential for malignancy
- can also be angiosarcomas – after previous radiation

Lymphoma: rare

Other
- papillary, medullary, mucinous, and tubular cancers
- generally better prognosis

Treatment

Table 31. Breast Cancer Treatment by Stage

Stage	Primary Treatment Options	Adjuvant Systemic Therapy
0 (*in situ*) Tis, N0, M0	BCS + radiotherapy BCS alone if margins >1 cm and low nuclear grade Mastectomy* ± SLNB	Consider postoperative tamoxifen for ER+, trastuzumab for HER2+
I IA: T1, N0, M0 IB: T1, N1mi, M0	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	May not be needed; discuss risks/benefits of chemotherapy and tamoxifen
II A: T0, N1, M0 T1, N1, M0 T2, N0, M0 B: T2, N1, M0 T3, N0, M0	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	Chemotherapy for premenopausal women or postmenopausal and ER negative, followed by tamoxifen if ER+
III A: T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0 B: T4, N0, M0 T4, N1, M0 T4, N2, M0	Likely mastectomy + axillary node dissection + radiotherapy after chemotherapy (neoadjuvant)	Neoadjuvant therapy should be considered (i.e. preoperative) especially if not resectable chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. postoperative)
Inflammatory	Mastectomy + axillary node dissection + radiotherapy	Neoadjuvant therapy
IV any T, any N, M1	Surgery as appropriate for local control	Primary treatment is systemic therapy (i.e. chemotherapy) and/or hormone therapy

BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy
*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient's preference since choice of local treatment does not significantly affect survival if local control is achieved

PRIMARY SURGICAL TREATMENT

Breast Conservation Surgery (BCS)

- lumpectomy must be combined with radiation for survival equivalent to mastectomy
- contraindications include
  - high-risk of local recurrence (e.g. extensive malignant-type calcifications on mammogram), and multifocal primary tumours
  - failure to obtain tumour-free margins after re-excision
  - not suitable for radiation therapy (pregnancy, previous radiation, and collagen vascular disease)
  - large tumour size relative to breast

Mastectomy

- radical mastectomy (rare): removes all breast tissue, skin, pectoralis muscle, and axillary nodes
- modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
- simple mastectomy: removes all breast tissue and skin
- see Plastic Surgery, PL38 for breast reconstruction

Sentinel Lymph Node Biopsy (SLNB)

- performed in women with clinically node-negative invasive breast cancer and those with extensive DCIS who are undergoing mastectomy
- patients with clinically suspicious nodes should get U/S + FNA prior to decision to proceed with SLNB
- technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
- intraoperative frozen section evaluated can be considered
- proceed with ALND if >3 positive nodes, with 1-3 nodes whole breast radiation therapy may be an alternative
- 5% false negative rate

Axillary Lymph Node Dissection (ALND)

- perform in patients with:
  - locally advanced (T4a, b, c) or inflammatory breast cancer
  - clinically node-positive axilla, confirmed by FNA or core biopsy, in a patient for whom neoadjuvant chemotherapy is not planned
  - several other specific cases (sentinel or axillary nodes, which remain positive after neoadjuvant chemotherapy, axillary recurrence following previous breast cancer treatment, among others)
- side effects: risk of arm lymphedema (10-15%), especially if getting radiation therapy, decreased arm sensation, and shoulder pain

BCS can be offered to most women with stage I/II disease

There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I and II disease

Effect of Radiotherapy after Mastectomy and Axillary Surgery on 10 Year Recurrence and 20 Year Breast Cancer Mortality: Meta-Analysis of Individual Patient Data for 8135 Women in 22 Randomised Trials
EBCTCG (Early Breast Cancer Trialists' Collaborative Group)
Lancet 2014;383(9935):2127-2135
Study: Assessed the effect of radiotherapy in women with one to three positive lymph node(s) after mastectomy and axillary dissection in a meta-analysis of 8135 women in 22 trials.
Results: For 700 women with axillary dissection and no positive nodes, radiotherapy had no significant effect on local regional recurrence, overall recurrence, or breast cancer mortality. For 1314 women with axillary dissection and one to three positive nodes, radiotherapy reduced local regional, overall recurrence, and breast cancer mortality. 1133 of these 1314 women were in trials in which systemic therapy (cyclophosphamide, methotrexate, and fluorouracil, or tamoxifen) was given in both trial groups and radiotherapy again reduced local regional recurrence, overall recurrence, and breast cancer mortality. For 1772 women with axillary dissection and four or more positive nodes, radiotherapy reduced local regional recurrence, overall recurrence, and breast cancer mortality.
Conclusion: Post mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when systemic therapy was given.

ADJUVANT/NEOADJUVANT

Radiation
- indications
  - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy
  - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement

Hormonal
- indications
  - ER positive plus node-positive or high-risk node-negative
  - selective estrogen receptor modulators (SERM) if premenopausal (e.g. tamoxifen) or aromatase inhibitors if postmenopausal (e.g. anastrozole); optimal duration 5-10 yr
  - other options include ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), and androgens (e.g. fluoxymesterone)
  - palliation for metastatic disease

Chemotherapy
- indications
  - ER negative plus node-positive or high-risk node-negative
  - triple-negative disease (ER/PR and HER2-negative) - more common in younger and African-American women
  - ER positive and young age
  - stage I disease at high-risk of recurrence (high grade, lymphovascular invasion)
  - palliation for metastatic disease
  - for HER2 positive breast cancer, add trastuzumab ± pertuzumab to the chemotherapy regimen

Effect of Axillary Dissection vs. No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial
JAMA 2017;318(10):918-926
Purpose: Assessed whether the 10 yr overall survival of patients with sentinel lymph node metastases treated with breast-conserving therapy and sentinel lymph node dissection (SLND) alone without axillary lymph node dissection (ALND) is noninferior to that of women treated with axillary dissection.
Results: The 10 yr overall survival was 86.3% in the SLND alone group and 83.6% in the ALND group. The 10 yr disease-free survival was 80.2% in the SLND alone group and 78.2% in the ALND group. 10 yr regional recurrence did not differ significantly between the 2 groups.
Conclusion: Among women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases, 10-yr overall survival for patients treated with SLND alone was noninferior to overall survival for those treated with ALND.

FOLLOW-UP

Post-Treatment Follow-Up
- assessment and physical exam q3-6 mo x 3 yr, q6-12 mo x 2 yr, and annually thereafter
- following BCS mammography q6-12 mo; can reduce to annual once stable, no other routine imaging unless clinically indicated
- women who receive tamoxifen should have regular gynecologic follow-up (increased risk of endometrial cancer)

Local/Regional Recurrence
- recurrence in treated breast or ipsilateral axilla
- 1% per yr up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis
- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation
- overall survival of metastatic breast cancer is 36-60 mo

Surgical Endocrinology

Thyroid and Parathyroid

- see Endocrinology, E24

Thyroidectomy

- indications: some thyroid cancers or suspicious thyroid nodules, metastases to thyroid, large (substernal) or symptomatic thyroid goitre, toxic nodules, or some patients with definitive management of Graves' disease (not candidates for RAI). There are minimally invasive approaches to thyroid nodules including Scarless (Transoral)Thyroidectomy and RFA (Radiofrequency Ablation) of large symptomatic or hot thyroid nodules.
- preoperative workup: thyroid U/S for thyroid nodules, FNA for nodules ≥1 cm with suspicious U/S features or for most nodules ≥1.5 cm with lower suspicion U/S features, and CT neck for preoperative staging when advanced disease is suspected
- complications
  - lobectomy: recurrent laryngeal nerve palsy (hoarseness or swallowing issues), neck hematoma
  - total thyroidectomy: same as above plus hypoparathyroidism/hypocalcemia, bilateral RLN palsy (potentially requiring tracheostomy)
  - 20-75% of patients need thyroxine after lobectomy and 100% need thyroxine after total thyroidectomy

Parathyroidectomy

- elevated calcium found for any reason as an outpatient (but also incidental finding as inpatient) is likely primary hyperparathyroidism and should be investigated further
- indications: symptomatic primary hyperparathyroidism (osteoporosis/stones), asymptomatic primary hyperparathyroidism with specific laboratory criteria (profoundly elevated serum Ca^{2+}, hypercalciuria/asymptomatic kidney stones, Cr clearance <30% normal, <50 yr)
- contraindications: familial hypocalciuric hypercalcemia
- preoperative localization to find parathyroid adenoma. Localizing studies include: 99mTc sestamibi scanning with ± SPECT (single-photon emission computed tomography), U/S, contrast CT
- complications: recurrent/superior laryngeal nerve injury, postoperative hypocalcemia, infection, and bleeding

Adrenal Gland

- see Endocrinology, E33 and E40
- functional anatomy
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), and reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine)
- types of adrenal tumours: functional (e.g. Cushing's syndrome, Conn's syndrome, pheochromocytoma) or non-functional

INCIDENTALOMA

- adrenal mass discovered by investigation of unrelated symptoms/issues

Epidemiology

- benign adenoma (70-80%) > metastases to adrenal (22%) >> cyst carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, and kidney
- peak incidence of carcinoma: females ages 50-60, risk decreases with increasing age and male gender

Investigations

- CT: size >4-6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm), MRI is not as good as CT and does NOT need to be done after CT
- functional studies
  - pheochromocytoma: plasma metanephrines (highly specific and sensitive). If not available, 24 h urine catecholamines
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, AM aldosterone, AM plasma renin activity level, ARR (Aldosterone-Renin-Ratio). If inconclusive, saline suppression test if appropriate
  - not routinely - only if clinical suspicion: adrenal androgens (17-OH progesterone and DHEAS)
- FNA biopsy: NOT APPROPRIATE in most cases. Diagnostic adrenalectomy by high volume endocrine surgeon ideal if diagnostic uncertainty

Treatment
- functional tumour: resect
- non-functional tumour
  - >4 cm: consider resection
  - <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement
  - genetic testing important for ALL Pheochromocytoma/paragangliomas as >30% are related to genetic syndrome

Pancreas

INSULINOMA
- tumour that secretes insulin
- most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

Clinical Features
- Whipple's triad
- palpitations, trembling, diaphoresis, confusion, seizure, and personality changes

Investigations
- blood work: decreased serum glucose and increased serum insulin and C-peptide, pro-insulin
- CT, EUS, MRI: insulinomas evenly distributed throughout head, body, tail of pancreas

Treatment
- only 10% are malignant
- enucleation of solitary insulinomas may be done endoscopically
- tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

GASTRINOMA
- tumour secreting gastrin; cause of Zollinger-Ellison syndrome, associated with MEN1

Clinical Features
- abdominal pain, PUD, severe esophagitis
- multiple ulcers in atypical locations refractory to antacid therapy

Investigations
- blood work: serum gastrin levels (usually >1000 pg/mL), secretin stimulation test
- endoscopy: 90% of patients develop peptic ulcers
- CT, EUS, MRI: 70-90% found in Passaro's triangle (head of pancreas medially, 2nd portion of duodenum inferiorly, and the confluence of the cystic and CBD superiorly)
- somatostatin receptor scintigraphy scan

Treatment
- 50% are malignant
- surgical resection of tumour dependent on location
- non-surgical treatment: high dose PPI, octreotide (somatostatin analogs)
- radiation therapy may be considered for nonsurgical candidates

VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR
- tumour secreting VIP; commonly located in the distal pancreas and most are malignant when diagnosed

Clinical Features
- severe watery diarrhea causing dehydration, anorexia, weakness, and electrolyte imbalance (hypokalemia)

Investigations
- blood work: serum VIP levels
- CT, MRI, EUS

Treatment
- repletion of fluid and electrolytes
- somatostatin analogues
- surgical resection/palliative debulking

Whipple's Triad
- Symptomatic fasting hypoglycemia
- Serum glucose <2.8 mmol/L
- Relief of symptoms when glucose is administered

Zollinger-Ellison Syndrome
Characterized by gastric acid hypersecretion caused by secretion of gastrin from gastrinomas; patient experiences diarrhea and abdominal pain, as well as peptic disease and reflux disease

Hypertrophic Pyloric Stenosis
Non-bilious emesis in infants is the classic presentation

Rule of 2s for Meckel's Diverticulum
- **2**% of the population
- **2**:1 male-to-female ratio
- Symptomatic in **2**% of cases
- Found within **2** feet (10-90 cm) of the ileocecal (IC) valve
- **2** inches in length
- **2** inches in diameter
- **2** types of tissue (ileal or ectopic gastric, pancreatic)
- Often present by **2** y/o

Pediatric Surgery

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Hydrocele (see Urology, U32)	1-2% of live births Majority resolve spontaneous by 1 yr M:F=6:1 Prematurity	Communicating hydroceles: processus vaginalis connects peritoneum with tunica vaginalis, so peritoneal fluid flows freely between the two with potential for abdominal contents to enter groin (i.e. inguinal hernia) Noncommunicating hydroceles: processus vaginalis is closed and more fluid produced than absorbed in tunica vaginalis; in older children, may be secondary to testicular pathology (e.g. reactive hydrocele)	Painless scrotal mass Communicating hydroceles increase in size with standing or valsalva, may be absent in the morning and large in the evening	Transillumination suggests hydrocele Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk	U/S if suspect pathology	Most resolve spontaneously by 1 yr Surgical repair if: Persistence >2 yr Pain Fluctuating in size which suggests communication Cosmetic reasons Infection	<2% recurrence
Hypertrophic Pyloric Stenosis	0.03-1.0% of live births Can present at 1-20 wk, most commonly at 6-8 wk M:F=4:1 Early erythromycin exposure (<13 d)	Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction Hypovolemia caused by emesis of gastric contents causes hypochloremic, hypokalemic metabolic alkalosis Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria	Projectile non-bilious vomiting Vomiting 30-60 min after feeds Hungry after vomiting Dehydration (variable severity)	Smooth oblong 1-2 cm "olive" mass palpable above umbilicus in the RUQ Visible left-to-right gastric contraction "waves" after feeding	Electrolytes (assess hypochloremia, dehydration) U/S shows pyloric length 17 mm, muscle thickness >4 mm Upper GI series (necessary only when U/S is unavailable or non-diagnostic) will show "string sign"	Fluid resuscitate with NS, correct electrolyte and acid/base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate NG tube decompression unnecessary Pyloromyotomy, open (Ramstedt vs. transumbilical or laparoscopic approach) is the definitive treatment Alternative therapies such as TPN/wait or atropine impractical due to long time course of effect	Pyloromyotomy curative
Congenital Diaphragmatic Hernias 3 types: Posterolateral (Bochdalek) Left-sided (85%) Right-sided (13%) Bilateral, rare, often fatal Anterior (Morgagni) Hiatus	1 in 2000 to 5000 live births Presents within hours of life although some cases of delayed presentation M=F >10% are associated with other congenital anomalies Prenatal diagnosis common	Combinations of small bowel, large bowel, stomach, and solid viscera (spleen, liver) may herniate into thorax Varying degrees of pulmonary hypoplasia and pulmonary hypertension possible	Early respiratory distress Cyanosis Scaphoid abdomen Prenatal diagnosis	Decreased air entry ± bowel sounds in the chest Displaced heart sounds	Prenatal US/MRI ABG CXR (bowel loops in hemithorax, shifted heart) Echocardiography Genetic consultation if warranted	Intubate/ventilate Orogastric suction Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extracorporeal membrane oxygenation) Surgical repair after stable by hernia reduction and closure of diaphragmatic defect open vs. thoracoscopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect	Better outcomes in later presentations Neurodevelopmental impairment Hearing deficit (40%) Associated GERD MSK defects chest wall and scoliotic defects as potential complications of thoracotomy Long-term surveillance for potential recurrence Failure to thrive Chronic lung disease if severe hypoplasia
Meckel's Diverticulum Most common remnant of vitelline duct that connects yolk sac with primitive midgut	1-3% of population M:F=3:1 Present most frequently during first 5 yr of life Symptomatic in 2% of cases	Failure of vitelline duct to regress 5-7 wk *in utero*; 50% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphalomesenteric fistula, umbilical sinus, umbilical cyst, and fibrous band	BRBPR (heterotopic gastric mucosa in Meckel's causing mucosal ulceration and bleeding in adjacent small bowel mucosa) Abdominal sepsis (Meckel's diverticulitis ± perforation) Small bowel volvulus around fibrous band Intestinal obstruction symptoms	Tenderness and distension (lower abdomen) near umbilicus	AXR Meckel scan: scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 85%, specificity 95%)	Stabilize, resection by laparotomy or laparoscopy ± incidental appendectomy	Resection curative
Malrotation	1 in 500 live births 1/3 present by 1 wk of age, 3/4 by 1 mo of age, 90% by 1 yr of age M:F=1:1 Higher incidence among patients with cardiac anomalies or heterotaxy syndromes	Failure of gut to normally rotate around SMA with associated abnormal intestinal attachments and anatomic positions Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high-risk for volvulus)	Cardinal sign: bilious emesis (especially if abdomen nondistended) If bilious emesis with distended abdomen, consider surgical exploration to rule out volvulus Rectal bleed (late/ominous signs) Intermittent symptoms	Bilious drainage from NG tube Tachycardic, pale Diaphoretic Flat abdomen Tenderness	AXR: proximal SBO, double-bubble sign, intestinal wall thickened Immediate UGI: dilated duodenum, duodenojejunal segment (Ligament of Treitz) right of midline and not fixed posteriorly over spinal column, "corkscrew" sign indicating volvulus U/S: "whirlpool" sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies	IV antibiotics Fluid resuscitation EMERGENT LAPAROTOMY Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd's bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide congenital adhesions), ± appendectomy Positioning the bowel into non-rotation (SBO in right abdomen, LBO in left abdomen)	Mortality related to length of bowel loss: 10% necrosis 100% survival rate, 75% necrosis 35% survival rate Recurrence 2-6%

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Gastroschisis	1 in 2000 live births Antenatal diagnosis common Increased risk with younger maternal age and associated with IUGR Rate slightly higher in male infants Smoking	Defect of abdominal wall near umbilicus, with free extrusion of intestine into amniotic cavity No specific environmental factor identified Defect in embryogenesis unclear	Not associated with genetic syndromes 10% with intestinal atresia Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel	Hollow viscera (stomach, small and large bowels) Defect lateral to cord (usually right) Bowel may be inflamed, thickened, matted, foreshortened Defect size variable	Prenatal U/S Elevated MS-AFP	NG tube decompression IV fluids IV antibiotics Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo May have bowel dysmotility requiring motility medications	>90% survival rate
Omphalocele	1 in 5000 live births Antenatal diagnosis common Lower gestational age Increased maternal age M:F=1.5:1	Defect of abdominal wall and umbilical ring, with extrusion of sac-covered viscera (amnion, Wharton's jelly, peritoneum) through the umbilical ring Duhamel's theory failure of body wall morphogenesis Commonly associated with rotational abnormalities of the intestine	30-70% associated with genetic syndromes (e.g. Pentalogy of Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome, Trisomy 18) Associated pulmonary hypoplasia	Hollow viscera (stomach, small and large bowels, often liver) Sac present with cord attached	Prenatal U/S Elevated MS-AFP	NG tube decompression IV fluids, IV antibiotics Small defect (<2 cm): Primary closure Medium (2-4 cm) and large (>4 cm) defects: silver sulfadiazine coupled with compression dressing (to allow epithelialization and gradual reduction) or Silon Silo Pouch, followed by future repair ± mesh	40-70% survival rate Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles
Umbilical Hernias	Incidence 2-14% Increases with prematurity Decreases with increasing age	Incomplete closure of peritoneal and fascial layers within umbilicus by 4 yr Hernia is peritoneum-lined and skin-covered Size of fascial defect determines chances of spontaneous closure	Majority asymptomatic Majority (95%) spontaneously resolve by age 4 Incarceration prior to age 5 very rare Most symptoms occur in late adolescence or adulthood	Protrusion from umbilicus Different from less common abdominal wall hernias that do not spontaneously resolve (e.g. epigastric hernias) Most defects >1.5 cm in infancy will not close spontaneously	None if uncomplicated	Repair if not spontaneously closed by age 5 Earlier repair of large "proboscoid" hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect	Rarely become incarcerated Low risk of recurrence
Intestinal Atresia	Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or "double-bubble" sign on x-ray for duodenal atresia Decreased with increasing age	Duodenal failure of bowel to recanalize after endodermal epithelium proliferation (wk 8-10) Jejunal/ileal acquired as a result of vascular disruption → ischemic necrosis → resorption of necrotic tissue → blind distal and proximal ends Colonic mechanism unknown, thought to be similar to small bowel atresia	Gastric distension and vomiting (usually bilious) Duodenal may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal, and vertebral anomalies), 24-28% have Down syndrome Jejunal/ileal within 2 d of birth, may be associated with CF Colonic within 3 d of birth	Complete physical Special attention to abdominal exam, perineum, and anus Include evaluation of respiratory distress and signs of volume depletion Congenital anomalies Jaundice	Contrast enema ± UGI with small bowel follow through (SBFT) Group and screen INR and PTT if for surgery	NPO NG tube decompression Fluid resuscitation TPN Broad spectrum antibiotics Duodenal duodenoduodenostomy or duodenojejunostomy Jejunal/ileal primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures Colonic primary anastomosis	Long-term survival: Duodenal 86% Jejunal/ileal 84% Colonic 100%
Congenital Aganglionic Meirschsprung's Disease	1 in 5000 births M:F=3:1 to 4:1, approaches 1:1 when whole colon involved Can have aganglionosis of small bowel as well Familial Hirschsprung's in <5% of cases	Defect in migration of neurocrest cells to intestine resulting in aganglionic bowel that fails to peristalse and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively Starts in the rectum and variable involvement proximally; RET mutation	Failure to pass meconium spontaneously within 48 h of life (95% pass meconium within 24 h, 5% within 48 h) Symptoms of bowel obstruction: abdominal distension, constipation, bilious emesis Enterocolitis/sepsis Failure to thrive	± Abdominal distension Squirt/blast sign	Rectal biopsy (gold standard) look for aganglionosis and neural hypertrophy AXR Contrast enema to find narrow rectum and transition zone Anal manometry unreliable in infants classic finding is absence of rectoanal inhibitory reflex	Duhamel pull-through procedure: surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis	Most have normal/near-normal anorectal function Complications: fecal incontinence and constipation, postoperative enterocolitis (medical emergency if progresses to sepsis)
Cryptorchidism	Most common congenital abnormality of the GU tract 2-5% of term males most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend Suspect in prematurity	Idiopathic Descent is mediated by INSL3 and testosterone Descent usually begins at 28 wk	Palpable testicle within inguinal canal or testicle which can be milked down into the scrotum (called retractile testis) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities	Scrotal asymmetry Bi-annual testicular exam with palpation Distinguish truly undescended testis from retractile testis (which is "high" testis due to hyperactive cremasteric muscles)	Depends on age of presentation Older child: LH, FSH, Müllerian inhibiting substance, hCG stimulation test for gonadotropin production Infant: U/S, FSH, LH, karyotype, MIS, 17-hydroxy-progesterone If non-palpable: exam under anesthesia, exploratory laparoscopy	hCG to stimulate testosterone production and descent Orchidopexy especially if undescended by age 6 mo-2 yr	Orchidopexy Decreased risk of torsion and blunt trauma to testicle No effect on malignant potential of testicle Descent can preserve spermatogenesis if performed by 1 yr

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Intussusception	Most common cause of bowel obstruction between 6-36 mo 26 in 100,000 newborns M:F=3:2 Pathologic lead points: enlarged Peyer's patches due to viral infections of the GI tract, polyps, Meckel's diverticulum CF, lymphoma and IBD may increase risk	Usually idiopathic Usually starts at ileocecal junction Telescoping of bowel into itself causing an obstruction and vascular compromise	Acute onset abdominal pain Episodic "colicky" pain Vomiting ± bilious Abdominal mass Currant-jelly stool suggests mucosal necrosis and sloughing	Abdominal exam Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness Signs of bowel obstruction: distended abdomen Look for localized peritonitis which suggests transmural ischemia	AXR for signs of bowel obstruction or perforation U/S if suspect pathology	If peritonitis, consider operative management Non-operative management involves reduction via air contrast enema Operative reduction (open or laparoscopically) Resection of involved colon if failure to reduce or bowel appears compromised	10% recurrence rate If recurrent = more likely non-idiopathic If successfully reduced by enema in older children, allow 2 wk resolution of edema before performing SBFT to rule out pathologic lead points
Tracheoesophageal Fistula (TEF)	1 in 3000 to 1 in 4500 live births Typically occurs with esophageal atresia	Defect in the lateral septation of the foregut into the esophagus and trachea causing connection between the esophagus and trachea Associated anomalies in 50%: VACTERL association	Varies with type of fistula May have history of maternal polyhydramnios May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds, respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth, and nose that return after suctioning	Abdominal distention	X-ray: anatomic abnormalities, NG tube curled in pouch	Investigate for other congenital anomalies Early repair by surgical ligation to prevent lung damage and maintain nutrition and growth	Complications: pneumonia, sepsis, reactive airways disease Following repair: esophageal stenosis and strictures at repair site, GERD, and poor swallowing (i.e. dysphagia, regurgitation)
Inguinal Hernias	5% of all term newborns 2x risk and more likely bilateral if pre-term M:F=4:1 Low birth weight increases risk 1/5 inguinal hernias will become incarcerated if patient is <1 yr Incarceration is more common in females Associated with other conditions: androgen insensitivity, connective tissue diseases	All infant hernias are indirect: descent of intra-abdominal contents through the internal inguinal ring through a patent tunica vaginalis Inguinal hernia can be reducible, incarcerated (unreducible), or strangulated	Most common presentation: painless intermittent mass in groin, may also note extension into scrotum (scrotal mass in absence of inguinal mass is a hydrocele) If incarcerated: tender, vomiting, firm mass, erythema then cyanosis of mass may be noted	Palpate for "bag of worms" - suggests possible testicular varicocele Biannual testicular exam + palpation along inguinal canal to evaluate for any masses "Silk sign" palpable thickening of cord Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen Must always try reduction to confirm that hernia is not incarcerated	Physical exam is gold standard U/S only if physical exam uncertain (e.g. in small infants where exam can be difficult)	Manual reduction in the ER to relieve acute symptoms For reducible hernia: repair within a few wk (if <1 yr) vs. elective repair (if >1 yr) For incarcerated hernia: repair immediately (emergency) Herniorrhaphy (laparoscopic or open) definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias	Risk of recurrence after surgical reduction <3%, higher if repair done in premature infants or if hernia was incarcerated/ strangulated

All inguinal hernias of infancy and childhood require repair at the earliest convenience; emergent repair if incarcerated/strangulated

Skin Lesions

- see Dermatology, D8; Emergency Medicine, ER43; Plastic Surgery, PL5

Common Medications

Types	Drugs and Dosing
Antiemetics	dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6 h prn prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM BID-TID prn metoclopramide (Maxeran®) 10 mg IV/IM q2-3 h prn, 10-15 mg PO QID (30 min before meals and QHS) ondansetron (Zofran®) 4-8 mg PO q8 h prn granisetron (Kytril®) 1 mg PO BID (for nausea from chemotherapy/radiation)
Analgesics	acetaminophen ± codeine (Tylenol® #3/plain) 1-2 tabs q4-6 h PO/PR prn hydromorphone 1-2 tabs PO q4 h prn, 0.5-2 mg IV q3-4 h prn ibuprofen 200-400 mg PO q4-6 h prn morphine 2.5-10 mg IM/SC q4-6 h prn + 1-2 mg IV q1 h prn for breakthrough ketorolac (Toradol®) 30-60 mg IM/IV q6 h prn acetaminophen/oxycodone (Percocet®) 325/5 mg, 1-2 tabs PO q4-6 h prn
DVT Prophylaxis	heparin 5000 units SC BID; if cancer patient, then heparin 5000 units SC TID/BID dalteparin (Fragmin®) 5000 units SC daily enoxaparin (Lovenox®) 40 mg SC daily
Antidiarrheals	loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO QID
Laxatives	sennosides (Senokot®) 1-2 tabs QHS docusate sodium (Colace®) 100 mg PO BID glycerine suppository 1 tab PR prn lactulose 15-30 mL PO QID prn milk of magnesia (MOM) 30-60 mL PO QID prn bisacodyl (Dulcolax®) 10-15 mg PO prn
Sedatives	zopiclone (Imovane®) 5-7.5 mg PO QHS prn lorazepam (Ativan®) 0.5-2 mg PO/SL QHS prn
Antibiotics	cefazolin (Ancef®) 1 g IV/IM on call to OR or q8 h – GP except *Enterococcus*, GN only *E. coli, Klebsiella*, and *Proteus* cefalexin (Keflex®) 250-500 mg PO QID – Listeria, GP except *Enterococcus*, GN only *E. coli, Klebsiella*, and *Proteus* ceftriaxone 1-2 g IM/IV q24 h broad coverage including Pseudomonas ampicillin 1-2 g IV q4-6 h – *Listeria*, GP (*Enterococcus*) except *Streptococcus* and *E. coli*, oral anaerobes
Bacteroides	gentamicin 3-5 mg/kg/d IM/IV divided q8 h; monitor creatinine, gentamicin levels GN including *Pseudomonas* ciprofloxacin 400 mg IV q12 h, 500 mg PO BID – GN including *Pseudomonas* metronidazole (Flagyl®) 500 mg PO/IV BID (500 mg PO TID for *C. difficile*) – anaerobes clindamycin 600-900 mg IV q8 h, 150-400 mg PO QID – GP except *Enterococcus*, anaerobes piperacillin/tazobactam 3.375 g IV q6 h – GP, GN, and anaerobes vancomycin 1g IV q12 h – GP and MRSA sulfamethoxazole/trimethoprim DS (Septra®) PO BID – GP, GN including *Nocardia*
Over-the-Counter Medications	bismuth subsalicylate (Pepto-Bismol®) 2 tabs or 30 mL PO q30 min-1 h up to 8 doses/d side effects: black stools, risk of Reye's syndrome in children ASA + citrate + bicarbonate (Alka-Seltzer®) 2 tabs in 4 oz water PO q4 h prn, max 8 tabs aluminum hydroxide + magnesium hydroxide (Maalox®) 10-20 mL or 1-4 tabs PO prn calcium carbonate (Tums®) 1-3 g PO q2 h prn calcium carbonate and magnesium hydroxide (Rolaids®) 2-4 tabs PO q1 h prn, max 12 tabs/d

Landmark General and Thoracic Surgery Trials

Trial Name	Reference	Clinical Trial Details
GROIN HERNIAS		
Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias	JAMA Surg 2013;148:1043-1048	**Title:** Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias **Purpose:** To compare outcomes of patients undergoing laparoscopic ventral hernia repair (LVHR) vs. open ventral hernia repair (OVHR). **Methods:** Single centre, retrospective study of 532 consecutive patients who underwent an elective primary ventral hernia (PVH) repair. The outcomes of the LVHR and OVHR were compared in terms of the primary outcomes of interest SSI, hernia recurrence, and bulging. **Results:** 79 patients with LVHR matched to 79 patients with OVHR with mesh with a median follow-up of 56 mo. LVHR was associated with fewer SSIs (7.6% vs. 34.1%) but more cases of bulging (21.5% vs. 1.3%) and port-site hernia (2.5% vs. 0.0%). No differences in recurrence were observed. **Conclusions:** LVHR is associated with fewer SSIs but more clinical cases of bulging and risk of developing a port-site hernia, compared to OVHR.
ACUTE CHOLECYSTITIS		
Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial	BMJ 2018;363:k3965	**Title:** Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial **Purpose:** To assess whether laparoscopic cholecystectomy is superior to percutaneous catheter drainage in high risk patients with acute calculous cholecystitis. **Methods:** 142 patients were randomized to either the laparoscopic cholecystectomy group or to the percutaneous catheter drainage group. **Results:** Although rate of death did not differ significantly between the laparoscopic cholecystectomy and percutaneous catheter drainage group, the complication rate in the laparoscopic cholecystectomy was significantly lower than that of the percutaneous catheter drainage (12% vs. 65%). The drainage group compared to the cholecystectomy group required reintervention at a higher rate, had recurrent biliary disease more frequently, and had longer lengths of stay. **Conclusions:** Laparoscopic cholecystectomy compared with percutaneous catheter drainage reduced the rate of major complications in high risk patients with acute cholecystitis.
BREAST CANCER		
10 Year Survival after Breast-Conserving Surgery Plus Radiotherapy Compared with Mastectomy in Early Breast Cancer in The Netherlands: A Population-Based Study	Lancet Oncol 2016;17(8):1158	**Title:** 10 Year Survival after Breast-Conserving Surgery Plus Radiotherapy Compared with Mastectomy in Early Breast Cancer in The Netherlands: A Population-Based Study **Purpose:** To evaluate 10 yr overall and breast cancer-specific survival after breast-conserving surgery plus radiotherapy compared with mastectomy in Dutch women with early breast cancer. **Methods:** Population study of women from the Netherlands Cancer Registry diagnosed with primary, invasive, stage T1-2, N0-1, M0 breast cancer, undergoing either breast-conserving surgery plus radiotherapy or undergoing mastectomy. **Results:** Breast-conserving surgery plus radiotherapy showed improved 10 yr overall and relative survival compared with mastectomy in early breast cancer, but 10 yr distant metastasis-free survival was improved with breast-conserving surgery plus radiotherapy compared with mastectomy in the T1N0 subgroup only, indicating a possible role of confounding by severity. **Conclusions:** Breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to survival and may influence treatment decisions for patients.

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GM Geriatric Medicine

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Acronyms

ACEI	angiotensin converting enzyme inhibitor	ESAS	Edmonton Symptom Assessment Scale	MAR	medication administration record	POA	power of attorney
ADL	activities of daily living	ESR	erythrocyte sedimentation rate	MMSE	Mini Mental Status Examination	PPS	Palliative Performance Scale
ADR	adverse drug reaction	GABA	gamma-aminobutyric acid	MS	multiple sclerosis	PR	per rectal
BADL	basic activities of daily living	GCA	giant cell arteritis	MSK	musculoskeletal	PTH	parathyroid hormone
BPH	benign prostatic hypertrophy	GERD	gastroesophageal reflux disease	NE	norepinephrine	PSW	personal support worker
BUN	blood urea nitrogen	GFR	glomerular filtration rate	NP	nurse practitioner	PUD	peptic ulcer disease
CBT	cognitive behavioural therapy	IADL	instrumental activities of daily living	NPIAP	National Pressure Injury Advisory Panel	PVD	peripheral vascular disease
CGA	comprehensive geriatric assessment	IBD	inflammatory bowel disease	NSTEMI	non-ST elevation myocardial infarction	RA	rheumatoid arthritis
CKD	chronic kidney disease	IBS	irritable bowel syndrome	NYD	not yet diagnosed	SNRI	serotonin-norepinephrine reuptake inhibitor
CNS	central nervous system	INR	international normalized ratio	OTC	over the counter	SSRI	selective serotonin reuptake inhibitor
CO	cardiac output	LOC	level of consciousness	PCI	percutaneous coronary intervention	TIA	transient ischemic attack
CrCl	creatinine clearance	LV	left ventricle			TCA	tricyclic antidepressant
						UI	urinary incontinence

Physiology and Pathology of Aging

Holistic Considerations for Aging

- aging results from the impact of the accumulation of a wide variety of molecular and cellular damage over time
- some of these changes are specific to the tissues of certain organs, whereas others occur over a number of organ systems
- normal age-related changes represent biologic processes common to everyone as they age; however, the rate and extent is extremely heterogeneous; thus, for the same chronological age, individuals may present with a different biological or phenotypic age or frailty level
- common geriatric syndromes are associated with advanced age. Often, there are many factors contributing to certain geriatric syndromes, such as falls and frailty, as opposed to a single cause

The table below outlines the physiological changes that occur with aging and their organ specific impacts. In addition, it outlines pathological conditions occurring in greater frequency in older adults. Physiological changes may predispose older adults to pathological conditions; however, unlike normal changes of aging, not all older adults will develop pathological changes associated with aging.

Table 1. A Systems-Based Analysis of Potential Changes That Can Occur with Aging

System	Physiological Changes	Impact of Physiologic Changes (Normal Aging)	Pathological Changes Occurring Frequently with Older Adults
Neurologic	Decreased brain mass and cerebral blood flow Increased white matter changes Reduced number of neurons Reduced action potential speed	Mild impact on working memory and processing speed Reduced sleep time Reduced fine-motor control Reduced reflex response	Insomnia, neurocognitive disorders (e.g. Vascular dementia, Alzheimer's disease), stroke
Senses	Eyes: thickened lenses, reduced pupil diameter, increased lipid infiltrates, decreased lacrimal gland secretion ENT: reduced saliva, atrophied hair cells, reduced cochlear and inner ear neurons, reduced ossicular articulation	Eyes: reduced visual acuity, dark adaptation ENT: reduced sense of smell and taste, reduced detection of higher frequency sounds (presbycusis – sensorineural hearing loss), reduced vestibular function	Increased glaucoma, cataracts, macular degeneration, tinnitus, vertigo, oral dryness
Cardiovascular	Increased left ventricular thickness and stiffness Increased vascular resistance Reduced pacemaker cells Decreased baroreflex and autonomic reflexes Decreased vessel elasticity, cardiac myocyte size and number, β-adrenergic responsiveness	Increased sBP, decreased dBP, HR, CO, wide pulse pressure Heart and blood vessels less responsive to physiological stress	Increased atherosclerosis, CAD, MI, CHF, HTN, arrhythmias, orthostatic hypotension
Respiratory	Increased tracheal cartilage calcification, mucous gland hypertrophy Decreased elastic recoil, increased residual volume, reduced vital capacity, forced expiratory volume Reduced chest wall compliance	Decreased arterial partial pressure of oxygen, decreased exercise tolerance, decreased pulmonary reserve	Increased COPD, pneumonia, pulmonary embolism
Gastrointestinal	Increased intestinal villous atrophy Decreased esophageal peristalsis, gastric acid secretion, liver mass, hepatic blood flow, calcium, and iron absorption	Reduced B_{12}, calcium and iron absorption	Increased dysphagia, cancer, diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction, malnutrition, weight loss
Renal and Urologic	Decreased renal mass and number of renal tubules and glomeruli, reduced renal blood flow Reduced nerve density and diminished detrusor function in bladder Reduced diurnal antidiuretic hormone	Decreased eGFR and concentration ability of kidney Increased urine pH Reduced hydroxylation of vitamin D Proteinuria Urinary frequency and urgency Nocturia	Increased urinary incontinence and urgency, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI, testicular atrophy, urinary retention

Functional Assessment (ADLs and IADLs)

ADLs: ABCDE-TT	IADLs: SHAFT-TT
Ambulating	**S**hopping
Bathing	**H**ousework
Continence	**A**ccounting/Managing finances
Dressing	**F**ood preparation
Eating	**T**ransportation
Transferring	**T**elephone
Toileting	**T**aking medications

Comprehensive Geriatric Assessment for Older Adults Admitted to Hospital
Cochrane DB Syst Rev 2017;CD006211
Purpose: To determine whether CGA can improve care provided to older adults admitted to hospital.
Results/Conclusions: Inpatient CGA increases likelihood that patients will be alive in their own homes at 3-12 mo follow-up (risk ratio (RR) 1.06, 95% CI 1.01-1.10), decreases the likelihood that patients will be admitted to a nursing home at 3-12 mo (RR 0.80, 95% CI 0.72-0.89), and results in little or no difference in dependence (RR 0.97, 95% CI 0.89-1.04). Evidence for cost-effectiveness of performing a CGA in older adults admitted to hospital is inconclusive due to imprecision and inconsistency among studies.

Comprehensive Geriatric Assessment for Community-Dwelling, High-Risk, And Frail Older People
Cochrane DB Syst Rev 2022;CD0012705
Purpose: Appraisal of the effectiveness of using the CGA for community-dwelling, high-risk, and frail older adults.
Results/Conclusions: CGA resulted in no difference in mortality during median follow-up at 12 mo (RR 0.88 95% CI 0.76-1.02), and concurrently no difference in nursing home admission (RR 0.93, 95% CI 0.76 to 1.14). CGA may decrease the risk of unplanned hospital admission over 14 mo of follow-up (RR 0.83 95% CI 0.70 to 0.99).

Table 1. A Systems-Based Analysis of Potential Changes That Can Occur with Aging

System	Physiological Changes	Impact of Physiologic Changes (Normal Aging)	Pathological Changes Occurring Frequently with Older Adults
Reproductive	Decreased androgen, estrogen, sperm count, vaginal secretion Decreased ovary, uterus, vagina, and breast size		Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis
Endocrine	Increased **NE**, **PTH**, insulin, vasopressin Decreased thyroid and adrenal corticosteroid secretion	Impaired stress response	Increased **DM**, hypothyroidism
MSK	Increased calcium loss from bone Decreased muscle mass/sarcopenia, cartilage, synovial fluid lubrication	Decreased strength (note: reduced motor strength on neurological examination is not expected) Joint stiffness and reduced joint capsule flexibility	Increased arthritis, bursitis, osteoporosis, muscle weakness with gait abnormalities, polymyalgia rheumatica
Integumentary	Atrophy of sebaceous and sweat glands Decreased epidermal and dermal thickness, dermal vascularity, melanocytes, collagen synthesis, elastin synthesis	Increased skin laxity, wrinkles, and skin stiffness, and easy bruising	Increased lentigo, cherry hemangiomas, pruritus, seborrheic keratosis, pressure injuries, skin cancer, onychomycosis, senile purpura, xerosis cutis
Immunologic	Decreased antigen-antibody affinity, decreased efficacy of neutrophils and macrophages, decreased numbers of B and T cells (excluding memory B and memory T cells)	Reduced response to new pathogens, reduced response to immunizations and increased need for boosters Blunted fever response and atypical presentation of infections which may lead to delayed care	Increased susceptibility to malignancies, infections, and autoimmune conditions
Psychiatric	Decreased processing speed, cognitive flexibility, visuospatial perception, working memory, and divided attention Loss of synaptic plasticity		Increased depression, dementia, delirium, suicidality, anxiety, sleep disruption

Framework for the Approach to the Older Adult

History: A Brief Geriatric Screen Using "The 5 M's Framework"

- **M**ind: consider mentation, dementia, delirium, and depression
  - consider more validated screening when concerns are raised from patients and/or family members/caregivers
  - consider asking if patients suffer from chronic pain
- **M**obility: observe for impaired gait and balance and consider fall injury prevention strategies
  - consider evidenced-based ways to reduce injuries: exercise, vision evaluation and treatment, home safety assessment, occupational therapy support, calcium and vitamin D supplementation
- **M**edications: monitor for polypharmacy, practice optimal prescribing, consider de-prescribing where possible, check adherence, check medication understanding from patient perspective, be cautious of adverse medication effects
- **M**ultimorbidity: use a bio-psycho-social approach to assess a patient's comorbidities
- **M**atters most: explore values and priorities (maintaining independence, preventing adverse events, optimizing comfort, prioritizing prolonged life)

Focused Geriatric Physical Exam

- general and vital signs: weight (signs of cachexia, unintentional weight loss), height (reduction may indicate vertebral compression fractures or osteoporosis), orthostatic vitals (blood pressure and heart rate)
- head and neck: test visual acuity, in-office hearing screen (whisper test), dentition, denture fit, lymphadenopathy, and neck masses
- cardiac: auscultate for arrhythmias, murmurs, extra heart sounds
- respiratory: auscultate, observe for SOB
- peripheral vascular exam: assess for arterial or venous insufficiency, inspect for edema and ulcers, palpate for diminished peripheral pulses
- dermatologic: look for premalignant/malignant lesions especially on sun-exposed areas, examine for pressure injuries in who are immobile, foot wounds in those with diabetes, neuropathy and peripheral vascular disease, examine for unexplained bruises or signs of elder abuse
- MSK: determine range of motion focused joint exam based on history
- gait: check footwear and fit of gait aids, assess gait systematically, Romberg for balance, and sit-to-stand test. Consider additional balance tests such as pull-back test, forward reach, tandem stance and gait
- neurologic: examine cranial nerves, tone, reflexes, sensation. Assess for signs of parkinsonism, tremor, and perform cerebellar testing

Presentations in Older Adults

Constipation

• see Gastroenterology, G28

Definition
• Rome IV Diagnostic Criteria (≥2 must be present in ≥1/4 of bowel movements for ≥3 mo with symptom onset ≥6 mo prior):
  ▪ straining
  ▪ hard stools
  ▪ sensation of incomplete evacuation
  ▪ use of manual maneuvers to facilitate defecation
  ▪ sensation of anorectal obstruction/blockage
  ▪ <3 bowel movements per wk
  ▪ patients must meet both of the following criteria:
    ◆ loose stool rarely present without the use of laxatives
    ◆ does not meet Rome IV criteria for IBS

Epidemiology
• chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation and 1/2 of patients >80 yr)
• in the elderly, chronic constipation may present as fecal impaction and overflow diarrhea

Etiology
• neurological: dementia, parkinsonism, autonomic dysfunction, spinal cord injuries
• metabolic: hypercalcemia, hypothyroidism, hypokalemia, hypomagnesemia
• nutritional: low dietary fibre, dehydration
• cancer/cancer related: colorectal cancer, post-radiation, tumour compression or bowel obstruction
• bowel related: IBS, IBD, strictures
• systemic diseases: systemic sclerosis, amyloidosis
• drugs associated with constipation:
  ▪ opioids
  ▪ psychotropics (e.g. antipsychotics, TCAs)
  ▪ anticholinergics (e.g. dimenhydrinate, diphenhydramine, TCAs, antimuscarinics for urinary incontinence)
  ▪ calcium channel blockers
  ▪ diuretics
  ▪ supplements (e.g. iron, calcium)
  ▪ immobility and non-optimal positioning)

Pathophysiology
• impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
• colorectal dysmotility

Alarm Symptoms
• fever
• hematochezia, blood in stool, positive fecal occult blood test / fecal immunochemistry test
• severe nausea/vomiting, severe abdominal pain
• abdominal/rectal mass
• obstipation
• new changes in bowel habits when age >50 yr
• unexplained anemia or iron deficiency on blood work
• acute onset
• severe constipation that is unresponsive to treatment
• weight loss >5kg in previous 6 mo
• change in stool caliber
• family history of colon cancer

Treatment
• non-pharmacological
  ▪ bowel training
  ▪ increase fibre intake to 20-30g per day (note: bulking agents, e.g. psyllium, Metamucil®, may worsen constipation in some), especially if insufficient fluid intake)
  ▪ ensure adequate fluid intake
  ▪ increase physical activity and optimize positioning for defecation (seated position, with knees at or above the level of hips)
• pharmacological
  ▪ see Figure 1
  ▪ discourage chronic laxative use
  ▪ review medication regime, reduce dosages or substitute
• see *Common Medications, GM*18

A Double-Blind, Placebo-Controlled Study of Prucalopride in Elderly Patients with Chronic Constipation
Neurogastroenterol Motil 2010;22(9):991-98
Purpose: To assess the efficacy, safety, and tolerability of prucalopride in chronically constipated elderly patients.
Results/Conclusions: The prucalopride dose range tested (1-4 mg daily) is effective at promoting bowel movements, minimizing constipation-associated symptoms, and improving quality of life. It is safe and well-tolerated in elderly patients with chronic constipation.

The Effect of Probiotics as a Treatment for Constipation in the Elderly: A Systematic Review
Arch Gerontol Geriatr 2017;71:142-49
Purpose: Evaluate the effectiveness of probiotics in treating elderly constipation, as an alternative to traditional drug-based treatments.
Results/Conclusions: Analysis of placebo-controlled RCTs suggested that administration of probiotics significantly improved constipation in the elderly by 10-40% compared to placebo. Further trials are required to elucidate optimal protocols of probiotic treatment regimens.

Treatment of Constipation in Older People
CMAJ 2013 May 14;185(8):663–67
Purpose: To summarize the treatments for constipation in older people and provide a guide to the assessment and management of constipation in older adults.
Results/Conclusions: The efficacy and safety of treatments for constipation in older people is presented and a step-wise approach to constipation in older adults is proposed.

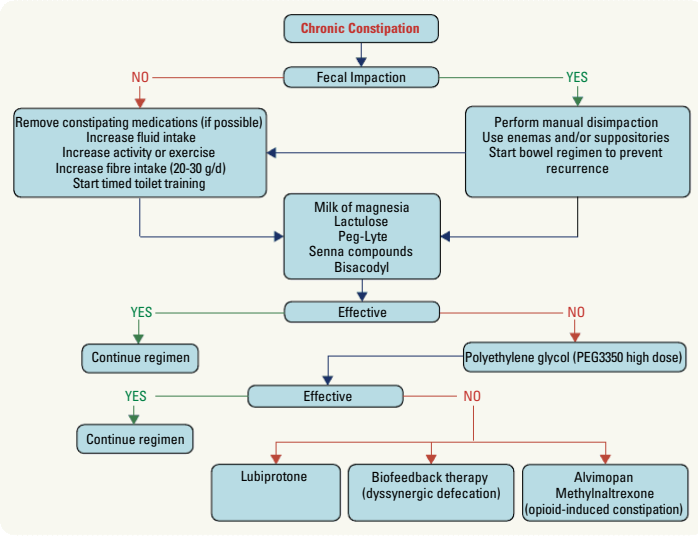

Figure 1. Treatment algorithm for the management of chronic constipation in older adults
Adapted from: Clin Interv Aging 2010;5:163-171

Delirium

• see Psychiatry, PS23 and Neurology, N21

Definition
• acute and potentially reversible disturbance in cognition, attention, or level of consciousness

Epidemiology
• delirium is especially common among patients in the ICU setting, postsurgical setting, and general medical setting
  ▪ up to 25% of patients after elective surgery
  ▪ 50% of patients after high-risk procedures (e.g. cardiac surgery, hip-fracture repair)
  ▪ up to 75% of mechanically ventilated patients in the ICU
• can affect all ages but is especially common in hospitalized older adults
  ▪ one-third of general medical patients >70 yr have delirium

Screening/Diagnostic Tools
• screened using the Confusion Assessment Method: delirium likely if 1 + 2 and either 3 or 4 are present
  1. acute onset and fluctuating course
  2. inattention
  3. disorganized thinking
  4. altered level of consciousness
• classified as: hyperactive, hypoactive, or mixed

Differential Diagnosis
• 3Ds (dementia, delirium, depression) can present with overlapping cognitive changes
• seizure
• stroke

Assessment
• history should ascertain patient's baseline cognitive function from informant
• ascertain course in hospital, obtain course of confusion with allied health
• review MARs for medications received in hospital, compare to home medications)
• substance use history, day of last use
• history and physical exams to assess for precipitating etiologies (DIMES)

Delirium in Older Persons: Advances in Diagnosis and Treatment
JAMA 2017;318(12):1161-74
Purpose: To provide overview of current state of diagnosis and treatment of delirium and identify promising areas for future research
Methods: Controlled vocabulary and keyword terms were searched in Ovid MEDLINE, Embase and the Cochrane Library with focus on studies conducted in elderly populations.
Results: 127 articles met inclusion criteria. High sensitivity and specificity brief screening tools and measures of delirium severity contribute to ability to diagnose, treat, risk stratify, and prognosticate patients. Nonpharmacologic approaches are effective for delirium prevention and recommended for delirium treatment. Pharmacologic treatment (antipsychotics, other sedatives) for agitation should only be used if the patient is at safety risk to themselves or others or is impeding medical treatment of the underlying cause.
Conclusion: Better screening and diagnosis of delirium leads to better risk stratification. Nonpharmacologic approaches of delirium prevention are effective, whereas pharmacological management of delirium is controversial.

Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review
Ann Intern Med 2019;171:485-95
Purpose: Evaluate with current literature the risks and benefits of antipsychotics in delirium management for hospitalized adults.
Study Selection: RCTs of antipsychotic vs. placebo or another antipsychotic, as well as prospective observational studies that report harms, are selected through searches on PubMed, Embase, CENTRAL, CINAHL, and PsycINFO from inception to July 2019. The review selected 16 RCTs and 10 observational studies of hospitalized adults.
Data Synthesis: No significant difference in sedation, delirium, hospital length-of-stay, or mortality between haloperidol and second-generation antipsychotics vs. placebo. No difference in mortality in direct comparisons between second-generation antipsychotics. While short term use of antipsychotics for delirium management does not appear to pose neurological harm, it poses a risk of QT prolongation.
Conclusion: The current evidence does not support the routine use of haloperidol or second-generation antipsychotics in delirium management for adult inpatients.

A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients
NEJM 1999;340:(9):669-676
Purpose: To evaluate the effectiveness of a multicomponent strategy for the prevention of delirium.
Conclusion: The multicomponent intervention lead to significant reductions in the number and duration of episodes of delirium in hospitalized older patients.

Assess for Precipitants "DIMES"

- **D**: drugs (consider prescribed, over the counter, overdose, intoxication, and withdrawal) (e.g. alcohol, benzodiazepine, nicotine, cannabis))
- **I**: infection (consider urinary tract, lungs, skin, bacteremia, CNS)
- **M**: metabolic disturbances (consider fluid imbalances, electrolyte abnormalities (hyponatremia, hypercalcemia), nutritional deficiencies (B12, B1), hepatic encephalopathy, hypothyroidism/ hyperthyroidism
- **E**: environmental (room changes, lighting, noise)
- **S**: structural insults (cardiovascular, CNS, pulmonary, GI, foley catheter, urinary retention, constipation)

Work-Up

- work-up is not universal and depends on possible causes based on history and physical exam:
  - drugs: toxicology screen, therapeutic drug-levels (Dilantin, carbamazepine, digoxin)
  - infection, infarction, inflammation: CBC, urinalysis, urine culture, blood culture, CXR, ECG, troponin, creatinine kinase
  - metabolic: basic and extended electrolytes, vitamin B12, TSH, LFT, toxicology screen, glucose, arterial blood gas/venous blood gas, creatinine
  - structural: neuroimaging, abdominal x-ray

Delirium Prevention in Older Adults

- orientation: orient to date/time, clocks and calendars visible in room
- cognitive stimulation: therapeutic activities, family visitation and education
- sleep enhancement: reduce interruptions at night, dim light., avoid sleep aids, stimulation during the day
- early and safe mobilization
- adequate nutrition and hydration: monitor fluid status, encourage oral hydration and nutrition, meal set-up and feeding assistance, use of dentures, up in chair to eat when possible
- optimal prescribing and avoid precipitating medications: multimodal pain control to limit opioid use, avoiding sedatives, anticholinergics. and antipsychotics, monitor for interactions and adverse events
- correction of sensory deficits: bring and use glasses & hearing aids, amplification devices
- reduce, monitor for and address acute insults: remove foleys as soon as possible, monitor for urinary retention and constipation, spirometry

Table 2. Differentiating the Three Ds of Cognitive Impairment

	Dementia	Delirium	Depression
Onset	Gradual or step-wise decline	Acute (hours to days)	Subacute (weeks to months)
Duration	Months to years	Days to weeks, may take months for deficits to fully resolve	Variable
Natural History	Progressive, usually irreversible, gradual loss of ADL/IADLs	Fluctuating, reversible High morbidity/mortality in very old Increased risk of subsequent development of dementia	Usually reversible May be recurrent
Level of Consciousness	Normal	Fluctuating Hyperactive/alert or depressed	Normal
Attention	Intact initially	Impaired	Possible reduced concentration
Orientation	Intact initially	Impaired, fluctuating	Intact
Behaviour	Disinhibition, personality change	Psychomotor agitation or retardation	Importuning, self-harm/suicide
Psychomotor	Normal	Fluctuates between extremes	Slowing
Sleep-Wake Cycle	Fragmented sleep at night	Reversed sleep-wake cycle	Early morning awakening
Mood and Affect	Can be unchanged Some may develop apathy, depression, anxiety, labile affect	Anxious, irritable, fluctuating	Depressed, flat affect, stable
Cognition	Gradually progressive decline in cognition Domains impacted depend on dementia subtype	Fluctuation Inattention predominant	Impaired concentration
Memory Loss	Short term memory impairment is predominant in Alzheimer's dementia	May have impaired short-term memory	Possible impairment in episodic memory

Evidence on Management of Delirium:

- see "Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review"
- see "Delirium in Older Persons: Advances in Diagnosis and Treatment"

Elder Abuse Prevalence in Community Settings: A Systematic Review and Meta-Analysis
Lancet Glob Health 2017;5:147-56
Purpose: Since quantitative syntheses of elder abuse prevalence are rare, the study aimed to quantify and understand prevalence variation at global and regional levels.
Methods: A comprehensive search strategy from 14 databases was employed to identify elder abuse prevalence studies in the community, published from inception to June 2015. Subgroup analysis and meta-regression were used to explore heterogeneity.
Results: 52 of the 38544 initially identified studies were eligible for inclusion, all of which were geographically diverse (28 countries). The pooled prevalence estimates were 11.6% for psychological abuse, 6.8% for financial abuse, 4.2% for neglect, 2.6% for physical abuse, and 0.9% for sexual abuse. Significant heterogeneity was found in associations with overall prevalence estimates, including sample size, income classification, and method of data collection, but not with gender.
Conclusion: Elder abuse is a neglected public health priority, especially compared with other types of violence. Elder abuse seems to affect 1 in 6 older adults worldwide, a figure totaling 141 million people.

Elder Abuse Screening Tools: A Systematic Review
J Adult Prot 2017;19:368-79
Context and Purpose: With high rates of morbidity and mortality, along with deleterious psychological harms, elder abuse is often difficult to detect. This study seeks to review currently available elder abuse screening tools.
Results: 11 of 34 full text studies met inclusion criteria and were included in the final analysis. Of these, three studies reported sensitivity and specificity while the remainder reported validity and reliability testing. Ultimately, the clinical environment will dictate the choice of screening tool.
Limitations: Variations in tool qualities and characteristics led to challenges in data synthesis. A further challenge was the lack of a gold standard screening tool for elder abuse, for evaluation of heterogeneity.
Conclusion: Research on screening tools remains hard-pressed in distinguishing those assessing suspected or actual elder abuse and those assessing risk factors for abuse. Although screening tools carry inherent limitations, they can be used to guide further assessments for an objective diagnosis.

Elder Abuse

Definition
- includes physical abuse, sexual abuse, emotional/psychological abuse, financial exploitation, and neglect
- elder abuse is a criminal offence under the Criminal Code of Canada and in most U.S. states

Epidemiology
- in Canada in 2019, almost 4518 seniors were victims of police-reported family violence
- the perpetrators of family violence against seniors were identified to be their grown child (34% of cases) and their spouses (26% of the cases)
- in older adults ≥60 yr, elder abuse is estimated to occur in 10% of patients
- insufficient evidence to include/exclude screening in the Periodic Health Exam

Risk Factors

Table 3. Risk Factors for Elder Abuse

Situational Factors	Social (e.g. isolation)
Victim Characteristics	Physical or emotional dependence on caregiver
	Lack of close family ties
	History of family violence
	Dementia or recent deterioration in health
Perpetrator Characteristics	Related to victim
	Dependency on older adult (e.g. financial dependency)

Screening Tools
- Elder Abuse Suspicion Index© (EASI©): a six-item questionnaire to raise a physician's level of suspicion for elder abuse and promote referral of possible victims for further assessment by social services

Management
- assess patient's decision-making capacity regarding any proposed intervention
- address imminent safety
- consider referral to local resources (home care, respite agencies, shelters, legal services, police services, government-supported elder abuse consultants)
- create emergency safety plan
- offer assistance with reporting abuse
- in Ontario, reporting elder abuse is mandatory when an older adult resides in a Long-term Care Home or a Retirement Home

Falls

Definition
- an event resulting in a person coming to rest inadvertently on a lower level, other than as a consequence of sudden paralysis, epileptic seizure, or overwhelming external force

Epidemiology
- approximately 20-30% of older adults ≥65 yr fall each year in Canada, prevalence increases with age
  - falls resulting in injury (e.g. broken/fractured bones, sprain/strain, concussion) were more likely to occur in women than men
  - 25% associated with serious and 1/3 of hospitalizations were associated with hip fractures
  - more than 1/3 of older adults are admitted to long-term care after hospitalization

Etiology
- intrinsic factors
  - age-related changes and diseases associated with aging: MSK (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), and metabolic (glucose, electrolytes)
  - orthostatic/syncopal
  - acute illness, exacerbation of chronic illness
- extrinsic factors
  - environmental (e.g. home layout, slippery surfaces, overcrowding, new environments)
  - side effects of medications, polypharmacy (>4 medications), and substance misuse (e.g. alcohol misuse)
- situational factors
  - activities (e.g. rushing to the toilet, walking while distracted)

History and Physical Exam
- falls history: pre-fall symptoms (chest pain, syncope, presyncope, palpitations), infectious symptoms, mechanisms, loss of consciousness, head trauma, neck/cervical spine trauma, post-fall (how long were they on the ground, who helped them up, post-fall confusion or amnesia)
- extended history: previous falls and/or gait instability, intrinsic, extrinsic and situational factors, associated symptoms, medication and alcohol use, change in medications

EASI©
For each of the 6 items below, indicate "yes," "no," or "did not answer." A response of "yes" on 1+ of questions 2-6 is concerning for elder abuse
Q.1-Q.5 asked of patient; Q.6 answered by doctor (Within the last 12 mo)

1 Have you relied on people for any of the following: bathing, dressing, shopping, banking, or meals?
2 Has anyone prevented you from getting food, clothes, medication, glasses, hearing aids or medical care, or from being with people you wanted to be with?
3 Have you been upset because someone talked to you in a way that made you feel shamed or threatened?
4 Has anyone tried to force you to sign papers or to use your money against your will?
5 Has anyone made you afraid, touched you in ways that you did not want, or hurt you physically?
6 Doctor: Elder abuse may be associated with findings such as: poor eye contact, withdrawn nature, malnourishment, hygiene issues, cuts, bruises, inappropriate clothing, or medication compliance issues. Did you notice any of these today or in the last 12 mo?

Yaffe MJ, Wolfson C, Lithwick M, et al. Development and validation of a tool to assist physicians' identification of elder abuse: The Elder Abuse Suspicion Index (EASI ©). J Elder Abuse Negl 2008;20(3):276-300.
https://www.mcgill.ca/familymed/research/projects/elder

Additional Canadian Resources for Management of Suspected Elder Abuse
Older Adults Safety Line: 24/7 confidential phone line providing information and referrals for older adults experiencing abuse
Advocacy Centre for the Elderly
Canadian Network for Prevention of Elder Abuse

Key Clinical History Findings in Falls Evaluation

SPLATT
Symptoms
Previous falls
Location of falls
Activity at the time of fall
Time of fall
Trauma

Impact of Medication Classes on Falls Risk in Geriatrics (Odds Ratios)

Antidepressants (1.68)
Neuroleptics/antipsychotics (1.59)
Benzodiazepines (1.57)
Sedatives/hypnotics (1.47)
Antihypertensive agents (1.24)
NSAIDs (1.21)
Diuretics (1.07)
β-blockers (1.01)

Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009:169(21):1952-1960

- have a witness present, if possible, for interview
- physical exam: orthostatic BP, injury screen, cardiac, visual acuity, examination of feet and footwear, gait assessment, Timed Up-and-Go Test, MSK, neurologic

Investigations

- CGA to identify potential causes
- investigations should be tailored based on history and physical examination. They might consist of:
  - CBC, electrolytes, BUN, creatinine, glucose, Ca^{2+}, TSH, vitamin B_{12}, urinalysis, cardiac enzymes, ECG, CT head (as directed by history and physical), coagulation profile
- bone densitometry (dual-energy x-ray absorptiometry) for osteoporosis screening in all women and men >65 yr

Interventions

- interventions depend on the identified intrinsic and extrinsic risk factors. First address any acute illness that precipitated the fall and treat any injuries or complications
- multidisciplinary, multifactorial, health and environmental risk factor assessment, and intervtion programs in the community
- muscle strengthening, balance retraining (e.g. Tai Chi) with appropriate assistive devices, and group exercise programs
- home hazard assessment and modification with potential for collaboration with occupational therapy (e.g. remove loose rugs and tripping hazards, add shower bars and stair railing, improve lighting)
- fitted gait aid
- taper or gradual discontinuation of psychotropic medication
- postural hypotension, heart rate, and rhythm abnormalities management
- eyesight (cataract surgery) and footwear optimization
- compression socks if venous stasis edema
- hip protectors
- prescription of vitamin D 1000 IU daily if vitamin D stores are low
- optimization of daily calcium intake via diet or calcium supplementation calcium in diet with 1200 mg of supplemental calcium advised if osteoporosis is a risk

Will My Patient Fall?
JAMA 2007;297:77-86
Purpose: To identify the prognostic value of risk factors for future falls among older patients.
Study Selection: Meta-analysis of prospective cohort studies of risk factors for falls.
Results: 18 studies were included. Clinically identifiable risk factors were identified across 6 domains: orthostatic hypotension, visual impairment, impairment of gait or balance, medication use, limitations in ADLs or IADLs, and cognitive impairment. The estimated pretest probability of falling at least once in any given yr for individuals ≥65 yr was 27% (95% CI 19-36%). Patients who have fallen in the past year are more likely to fall again (LR 2.3-2.8). Best predictors of future falls were disturbances in gait or balance (LR 1.7-2.4), while visual impairment, impaired cognition, and medication were not reliable predictors.
Conclusions: Screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past yr. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problem are at higher risk of future falls.

Frailty

Definition

- frailty: clinically-recognizable state of decreased reserve in older adults with increased vulnerability to acute stressors resulting from functional decline across multiple physiologic systems
- functional decline: progressive limitation in the ability to carry out basic functional activities
- frailty is associated with higher risk of in-hospital death, adverse events, length of stay, hospital re-admission, and newly dependent at discharge following critical illness

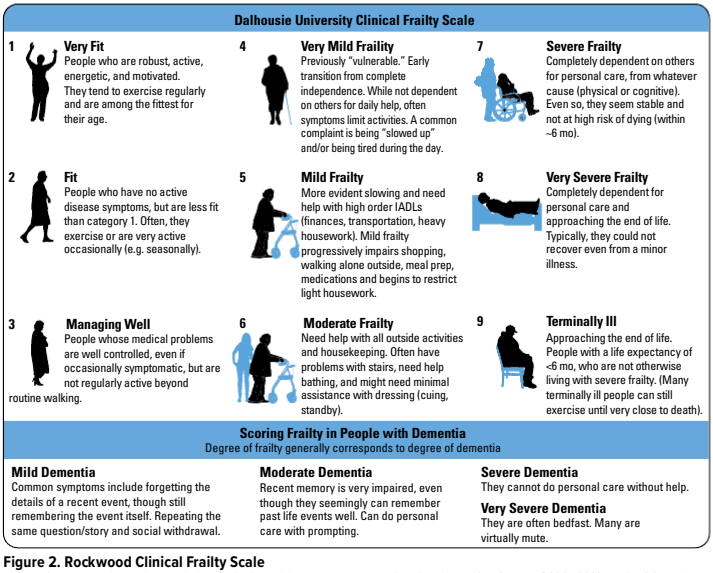
Dalhousie University Clinical Frailty Scale
1
Very Fit
People who are robust, active, energetic, and motivated. They tend to exercise regularly and are among the fittest for their age.
2
Fit
People who have no active disease symptoms, but are less fit than category 1. Often, they exercise or are very active occasionally (e.g. seasonally).
3
Managing Well
People whose medical problems are well controlled, even if occasionally symptomatic, but are not regularly active beyond routine walking.
4
Very Mild Frailty
Previously "vulnerable." Early transition from complete independence. While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up" and/or being tired during the day.
5
Mild Frailty
More evident slowing and need help with high order IADLs (finances, transportation, heavy housework). Mild frailty progressively impairs shopping, walking alone outside, meal prep, medications and begins to restrict light housework.
6
Moderate Frailty
Need help with all outside activities and housekeeping. Often have problems with stairs, need help bathing, and might need minimal assistance with dressing (cuing, standby).
7
Severe Frailty
Completely dependent on others for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 mo).
8
Very Severe Frailty
Completely dependent for personal care and approaching the end of life. Typically, they could not recover even from a minor illness.
9
Terminally Ill
Approaching the end of life. People with a life expectancy of <6 mo, who are not otherwise living with severe frailty. (Many terminally ill people can still exercise until very close to death).
Scoring Frailty in People with Dementia
Degree of frailty generally corresponds to degree of dementia
Mild Dementia
Common symptoms include forgetting the details of a recent event, though still remembering the event itself. Repeating the same question/story and social withdrawal.
Moderate Dementia
Recent memory is very impaired, even though they seemingly can remember past life events well. Can do personal care with prompting.
Severe Dementia
They cannot do personal care without help.
Very Severe Dementia
They are often bedfast. Many are virtually mute.

Figure 2. Rockwood Clinical Frailty Scale
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MODELS OF FRAILTY

Physical Frailty (PF) Phenotype (Fried et al.)
- Frail: ≥3 criteria; at-risk or pre-frail = 1 or 2 criteria
  1. shrinking: unintentional weight loss (baseline: >=10 lbs or 5% total body weight lost in prior yr)
  2. weakness: grip strength in lowest 20% (by gender, BMI)
  3. poor endurance: as indicated by self-report of exhaustion
  4. slowness: walking time/15 feet in slowest 20% (by gender, height)
  5. low activity: kcals/wk in lowest 20% (males: <383 kcals/wk, females: <270 kcals/wk)

Cumulative Deficit Approach (Rockwood et al.)
- balance between assets (e.g. health, attitudes, resources, caregiver) and deficits (e.g. illness, disability, dependence, caregiver burden) that determines whether a person can maintain independence in the community
- frailty index: number of deficits present/number of deficits possible

Etiology
- multifactorial: dysregulated immune, endocrine, stress, and energy response systems lead to development of clinical frailty

Table 4. Etiologies of Frailty

Etiology	Mechanism
Physiologic Changes with Aging	Sarcopenia (age-related loss of skeletal muscle and strength), decreased mass and increased stiffness of organs, decreased reserve capacity of systems
Immune System	Elevated levels of circulating interleukin-6, C-reactive protein, white blood cells, and monocytes associated with skeletal muscle decline Elevated clotting markers (factor VIII, fibrinogen, D-dimer) upregulates clotting cascade Chronic inflammation
Endocrine System	Sarcopenia via: Decreased growth hormone and IGF-1 Increased cortisol levels Decreased DHEA-S Decreased 25 (OH) vitamin D
Stress dysregulation of autonomic nervous system	
Age-related changes in renin-angiotensin system and mitochondria likely impact sarcopenia and inflammation	

Evidence-based Approach to the Frail Older Patient
- CGA
  - includes: past medical history, medications, allergies, social history, function, and geriatric review of systems (cognition, mood, sleep, pain, nutrition, falls, continence, vision/hearing, skin, and safety)
  - physical exam
  - investigations: CBC, electrolytes, TSH, vitamin B12, vitamin D, LFTs, extended electrolytes
- management
  - CGA to tailor management of geriatric syndromes (e.g. falls, cognitive impairment, incontinence)
  - physical activity programs, nutritional optimization, multicomponent interventions
  - interdisciplinary primary care
  - referral to Acute Care for Elders (ACE) unit for inpatients who are living with frailty
  - medication optimization
  - caregiver support

Immobility

Definition
- limitation in independent and voluntary physical movement of the body or one or more lower
- extremities associated with disability, increased frailty and risk of falls, decreased quality of life

Etiology and Risk Factors
- multifactorial; functional assessment in addition to comprehensive history-taking and interdisciplinary approach to care is crucial
- psychological
  - fear of falling, motivation, depression
- physical changes
  - MSK disorders: history of hip or leg fractures, osteoporosis, arthritis
  - neurologic disorders: stroke, Parkinson's disease, severe dementia, neuropathies
  - cardiovascular: CHF, angina secondary to CAD, claudication secondary to PVD
  - sensory: poor vision, decreased peripheral sensation/proprioception
- interpersonal/social factors

- environmental changes
  - iatrogenic (healthcare facilities)
  - deconditioning secondary to prolonged bed rest
  - inadequate mobility aids
  - poorly controlled chronic and acute pain

Complications
- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- MSK: atrophy, contractures, bone loss
- skin: pressure injuries
- psychological: sensory deprivation, delirium, depression

Incontinence

Fecal Incontinence

Definition
- involuntary or inappropriate passing of feces that impacts social functioning or hygiene
- severity can range from unintentional flatus to the complete evacuation of bowel contents
- there are three subtypes:
  1. passive incontinence: involuntary discharge of stool or gas without awareness
  2. urge incontinence: discharge of fecal matter in spite of active attempts to retain bowel contents
  3. fecal seepage: leakage of stool following otherwise normal evacuation

Epidemiology
- the incidence of fecal incontinence differs by setting: community (17-36%), hospital (16%), and nursing home (33-65%)
- risk factors: constipation, age >80 yr, female sex, UI, impaired mobility, dementia, neurologic disease

Etiology
- physiological changes with age >80 yr (e.g. decreased external sphincter strength, decreased resting tone of internal sphincter, weakened anal squeeze, increased rectal compliance, and impaired anal sensation)
- trauma (e.g. vaginal delivery, pudendal nerve damage, cauda equina)
- iatrogenic
  - surgical (e.g. anorectal surgery, lateral internal sphincterotomy, hemorrhoidectomy, colorectal resection)
  - radiation (e.g. pelvic radiation)
- neurogenic (e.g. neuropathy, stroke, MS, diabetic neuropathy)
- anorectal/colorectal diseases (e.g. rectal prolapse, hemorrhoids, IBD, rectocele, cancer)
- medication (e.g. laxative, anticholinergics, antidepressants, caffeine, muscle relaxants)
- cognitive (e.g. dementia, willful soiling with psychosis)
- constipation/fecal impaction

Investigations (if cause not apparent from history and physical)
- differentiate true incontinence from frequency and urgency
- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

Management
- physiological changes with age: medication management (antimotility agents (e.g. loperamide), diet/bulking agents for loose stool), increase fluid intake, biofeedback, retraining of pelvic floor muscles, surgery
- trauma: direct surgical repair or augmentation of the sphincters
- iatrogenic: surgical repair, artificial sphincters
- neurogenic: medication management, abdominal massage, digital stimulation for dysfunction, biofeedback and behavioural training, prevent autonomic dysreflexia in spinal injury
- anorectal/colorectal diseases: treat underlying cause (optimize IBD medications), surgical (e.g. mass removal, prolapse repair, hemorrhoid removal, colostomy)
- medication-related causes: stop laxatives, lower dose, or discontinue any other offending agents
- cognitive: regular defecation program in patients with dementia, psychiatric consult (optimize medications and cognitive function)
- constipation/fecal impaction: disimpaction, prevent impaction, enema, or rectal irrigation
- safety assessment: assess bathroom distance, fall prevention strategies, need for a bedside commode, liaise with occupational therapy if necessary

Urinary Incontinence

• see Urology, U6

Definition

- complaint of any involuntary loss of urine
- there are 4 subtypes:
  1. stress incontinence: leakage associated with physical strain
  2. urge incontinence: leakage associated with strong urge to urinate
  3. overflow incontinence: leakage associated with poor bladder emptying
  4. functional incontinence: leakage due to illness or disability not related to the urinary tract

Transient Causes of Incontinence

DIAPERS
Delirium
Infection
Atrophic urethritis/vaginitis
Pharmaceuticals
Excessive urine output
Restricted mobility
Stool impaction

Epidemiology

- 15-30% prevalence dwelling in community and at least 50% of institutionalized older adults
- morbidity: cellulitis, pressure injuries, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality
- risk factors: impaired mobility, falls, medications, depression, TIA/stroke, dementia, CHF, obesity

Etiology

- physiologic changes with age: (e.g. decreased bladder capacity)
- genitourinary diseases (e.g. cystitis, urethritis, BPH)
- neurogenic (e.g. cauda equina syndrome, stroke, MS)
- iatrogenic: (e.g. prostate surgery)
- trauma: (e.g. pelvic trauma, traumatic spinal cord injury)
- drugs (e.g. alcohol, loop diuretics, sedative hypnotics, GABAergic agents)
- cognitive (e.g. dementia, depression)
- functional impairment (e.g. arthritis, poor vision)

Investigations

- laboratory tests: urinalysis and urine culture, serum creatinine, BUN
- imaging: post-void residual, renal ultrasound
- other: voiding diary, pad test

Management

- lifestyle modification: avoid excessive fluid intake and alcohol
- pharmacologic: β-adrenergic agonists to reduce involuntary bladder contractions
- physiologic changes with age: pelvic muscle exercises, bladder training, biofeedback
- genitourinary diseases: treat underlying cause (empiric antimicrobial treatment for cystitis, α blockers/5-α reductase inhibitors for BPH)
- functional impairment: incontinence pads, environmental modification, personal assistance
- cognitive: referral to incontinence program if needed
- safety assessment: assess bathroom distance, fall prevention strategies, need for a bedside commode, liaise with occupational therapy if necessary

Malnutrition

Definition

- no uniformly accepted definition of malnutrition in older adults. One definition provided by the 2018 Global Leadership Initiative on Malnutrition requires a combination of one phenotypic and one etiologic finding:
  - phenotype
    - weight loss: >5% within past 6 mo or 10% beyond 6 mo
    - low BMI
    - reduced muscle mass measured by DXA, BIA, CT or MRI
  - etiology
    - reduced food intake
    - inflammation: from acute disease/injury or chronic disease-related
- other definitions include: hypocholesterolemia (<4.1 mmol/L), hypoalbuminemia (community: ≤38 g/L; hospital: ≤35 g/L), insufficient energy intake, fluid accumulation (e.g. edema), loss of subcutaneous fat, decreased hand-grip function

Etiology of Malnutrition in Older Adults

MEALS ON WHEELS
Medications
Emotional problems
Anorexia
Late-life paranoia
Swallowing disorders
Oral problems
Nosocomial infections
Wandering/dementia related activity
Hyperthyroid/hypercalcemia/hypoadrenalism
Enteric disorders
Eating problems
Low-salt/low-fat diet
Stones

Etiology

- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals, or feeding oneself due to functional impairment), substance use
- stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical: dental problems, dysphagia

- age-related changes: decreased thirst, decreased smell and taste, delayed gastric emptying causing early satiety, decreased ghrelin production
- mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

Clinical Features
- history
  - weight loss in 6 mo prior to examination
  - recent or chronic illness
  - constitutional symptoms (e.g. recent weight loss)
  - dietary intake in relation to usual pattern
  - depression, GI symptoms (e.g. anorexia, nausea, vomiting, diarrhea)
  - functional disability: impaired ADLs and IADLs, cognitive decline ("forgetting meals")
  - social factors: economic barriers, dental problems, and living situation (e.g. living alone)
  - substance use (e.g. alcohol, smoking, IV or recreational drug use)
- physical exam
  - BMI <23.5 in males and <22.0 in females should raise concern
  - muscle wasting, temporal wasting, presence of triceps skin fold
  - loss of subcutaneous fat
  - ankle or sacral edema, ascites
  - assess cognition

Investigations
- CBC, electrolytes, Ca^{2+}/albumin, Mg^{2+}, PO_4^{3-}, creatinine, LFTs (INR, bilirubin), vitamin B_{12}, folate, TSH, lipid profile
- if indicated by assessment, can consider urinalysis, ESR, CXR

Treatment
- direct treatment of underlying causes, encourage meals with family, friends or caregivers ("social eating")
- dietary modification: high calorie foods, oral nutritional supplementation with high protein supplementation preferred: patient specific meal replacement products (e.g. Ensure™, Glucerna™, Nepro™), vitamins/minerals (e.g. vitamin B12, calcium, vitamin D, thiamine)
- referral: speech language pathologist, nutritionist

Presbycusis

- see Otolaryngology, OT19

Presbyopia

- see Ophthalmology, OP8

Pressure Injuries

- see Plastic Surgery, *Pressure Ulcers*, PL17

Definition
- previously termed pressure ulcers/injuries, also termed decubitus ulcers
- any lesion caused by unrelieved pressure resulting in damage of underlying tissue; usually develops over bony prominences

Risk Factors
- extrinsic: friction, pressure, shear force, moisture
- intrinsic: immobility, malnutrition, comorbidities (e.g. DM, PVD, vasculitis, immunodeficiency, CHF), sensory loss
- geriatric: age-related skin changes, bedbound, cognitive impairment, chronic illness

Risk Assessment and Prevention of Pressure Ulcers
Ann Intern Med 2015;162:359-369
The American College of Physicians (ACP) strongly recommends advanced static mattresses or advanced static overlays for patients who are at an increased risk of developing pressure injuries. The ACP also recommends against using alternating air mattresses or alternating air overlays.

Table 5. NPIAP Staging System for Pressure Injuries

Stage 1	Localized area of nonblanchable erythema of intact skin (appearance may vary in darkly pigmented skin) Changes in sensation, temperature, or firmness may precede visual changes Colour changes do not include purple or maroon discolouration (may indicate deep tissue penetration injury)
Stage 2	Partial thickness loss of skin with exposed dermis Wound bed is viable, pink or red, moist, and may present as a serum-filled blister Adipose and deeper tissue not visible
Stage 3	Full thickness loss of skin; adipose tissue visible Slough and/or eschar may be visible Granulation tissue and epibole (rolled wound edges) often present
Stage 4	Full thickness skin and tissue loss Exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone Slough or eschar can be present on some parts of the wound bed Epibole, undermining, and/or tunneling often present
Unstageable Pressure Injury	Full-thickness skin and tissue loss; extent of tissue damage cannot be determined due to obstruction by slough or eschar
Deep Tissue Pressure Injury	Intact or nonintact skin with localized nonblanchable maroon or purple discolouration, or epidermal separation revealing dark wound bed or blood-filled blister Pain and temperature changes may precede skin colour changes Injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface

Source: Edsberg LE, Black JM, Goldberg M, et al. Revised National Pressure Ulcer Advisory Panel Pressure Injury Staging System: Revised Pressure Injury Staging System. J Wound Ostomy Continence Nurs 2016;43(6):585-597

Complications

- noninfectious: amyloidosis, heterotopic bone formation, perineal urethral fistula, pseudoaneurysm, Marjolin ulcer, systemic complications of topical treatment, complications of oral/IV treatments
- infectious: bacteremia/sepsis, cellulitis, osteomyelitis, septic arthritis, sinus tracts, abscess, endocarditis, meningitis

Prevention

- barrier cream to sacral area
- pressure reduction
  - frequent repositioning (q2 h in bed, q1 h in chair)
- support services (alternating-pressure mattresses/overlays, low-air-loss beds)
- optimizing nutritional status, encouraging mobility, and managing incontinence
- use validated pressure injury risk assessment (head-to-toe) tools on admission for those identified to be at risk for skin breakdown

Treatment

- optimize nutritional status
- minimize pressure on wound
- analgesia
- all ulcers with necrosis warrant debridement (mechanical, enzymatic, and autolytic are non-urgent forms of debridement, whereas sharp debridement is performed urgently due to risk of sepsis or cellulitis)
- dressing application (exudate absorbing, barrier products to reduce friction)
- maintain moist wound environment to enable re-epithelialization
- treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
- swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
- referral to Wound Care or Plastic Surgery
- consider other treatment options:
  - negative pressure wound therapy/vacuum-assisted closure
  - biological agents: application of fibroblast growth factor or platelet-derived growth factor to wound
  - non-contact normothermic wound therapy
  - electrotherapy

Driving Competency

Reporting Requirements

- physician-reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia, and Alberta, where it is discretionary
- British Columbia, Ontario: must refer for re-test at ≥80 yr
- in the U.S., varies by state

Conditions That May Impair Driving

Table 6. Conditions That Impair Driving

Alcohol	Patients with history of impaired driving and those with a high probability of future impaired driving should not drive until further assessed
	Alcohol dependence or alcohol use disorder: if suspected, should be advised not to drive
	Alcohol withdrawal seizure: must (1) receive favourable report from addictions counsellor post-treatment and (2) be in remission and/or remained abstinent for 12 mo
Blood Pressure Abnormalities	HTN: sustained BP >170/110 should be evaluated carefully
	Hypotension: sustained BP <90/60; if syncopal, discontinue driving until syncope is treated and preventable
Cardiovascular Disease	Suspected asymptomatic CAD or stable angina: no restrictions
	STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for 1 mo following hospital discharge
	NSTEMI with minor LV damage, unstable angina: no driving for 48 h if PCI or 7 d if no PCI performed
Cerebrovascular Conditions	TIA: should not be allowed to drive until a medical assessment is completed
	Stroke: should not drive for at least 1 mo; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual, or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure
COPD	Mild/moderate impairment: no restrictions
	Moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen
Cognitive Impairment/Dementia	Moderate to severe dementia is a contraindication to driving, defined as the "inability to independently perform 2 or more IADLs or any basic ADL"
	Patients with mild dementia should be assessed; if indicated, refer to specialized driving testing centre; if deemed fit to drive, re-evaluate patient every 6-12 mo
	Poor performance on MMSE, clock drawing, or Trails B suggests a need to investigate driving ability further
	MMSE score alone (whether normal or low) is insufficient to determine fitness to drive
Diabetes	Diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular, or cerebrovascular disease)
	Insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 mo
Drugs	Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants
	Degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving
Hearing Loss	Effect of impaired hearing on ability to drive safely is controversial
	Acute labyrinthitis, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves
Musculoskeletal Disorders	Physician's role is to report etiology, prognosis, and extent of disability (pain, range of motion, coordination, muscle strength)
Postoperative	Outpatient, conscious sedation: no driving for 24 h
	Outpatient, general anesthesia: no driving for ≥24 h
Seizures	First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head
	Epilepsy: can drive if seizure-free for 6 mo, on medication that does not impair ability to drive, and physician has insight into patient compliance (Ontario guideline)
Sleep Disorders	If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive
Visual Impairment	Visual acuity: contraindicated to drive if <20/50 with both eyes examined simultaneously
	Visual field: contraindicated to drive if <120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously

N.B. guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving

Key Factors to Consider in Older Drivers
SAFEDRIVE
Safety record
Attention (e.g. concentration lapses, episodes of disorientation)
Family observations
Ethanol use
Drugs
Reaction time
Intellectual impairment
Vision/Visuospatial function
Executive functions (e.g. planning, decision-making, self-monitoring behaviours)
Geriatrics 1996;51:36-45

Cognitive Tests and Determining Fitness to Drive in Dementia: A Systematic Review
J Am Geriatr Soc 2016;64(9):1904-1917
Purpose: To examine the relationship between cognitive tests and driving to determine whether a cognitive assessment can be implemented as a tool to examine driver safety.
Methods: Systematic review of 28 studies investigating the relationship between cognitive functioning and driving in individuals with dementia.
Results: Composite batteries comprising multiple individual tests from different cognitive domains consistently predicted driving performance for individuals with dementia. Scores on individual tests or tests of a single cognitive domain did not predict driver safety.
Conclusions: While studies consistently found composite batteries predicted driving performance, these tests were not clinically usable as they lacked the ability to discriminate between safe and unsafe drivers. Need development of a reliable, valid composite battery that can correctly determine driver safety in patients with dementia.

Hazards of Hospitalization

Table 7. Recommendations for Sequelae of Hospitalization in Older Patients

Sequelae	Recommendations
Malnutrition	No dietary restrictions (except diabetes and salt restriction if applicable), assistance, dentures if necessary, sitting in a chair to eat
Urinary Incontinence	Medication review, remove environmental barriers, discontinue use of catheter
Depression	Routine screening
Adverse Drug Event	Medication review
Confusion/Delirium	Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints
Pressure Injuries	Reactive air surface support services, daily inspection, repositioning every 2 h, nutrition
Infection	Early mobilization, remove unnecessary IV lines, catheters, NG tubes
Falls	Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review
Hypotension/Dehydration	Early recognition and repletion (ideally oral rehydration, if possible), access to water
Diminished Aerobic Capacity/Loss of Muscle Strength/ Contractures	Early mobilization
Decreased Respiratory Function	Incentive spirometry, physiotherapy
Functional Decline	Structured exercise, progressive resistance training, walking programs

Bell SP, Vasilevskis EE, Saraf AA, et al. Geriatric Syndromes in Hospitalized Older Adults Discharged to Skilled Nursing Facilities. J Am Geriatr Soc 2016;64(4):715–722

Healthcare Institutions

Table 8. Classification of Healthcare Services and Institutions

Institution/Service	Description
Home and Community Support Services	At-home support services offered to patients living at home independently or under the care of family members. These include professional healthcare services, personal care and support (ADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks)
Rehabilitation	Healthcare services offered in an institution to optimize patients' function, independence, and quality of life
Residential	Divided into short (<60-90 d/yr) and long (indefinite) stay
a) Older adults Affordable Housing	Seniors who live independently and manage their own care, but prefer to live near other older adults; usually has accessibility features; rent is adjusted based on income
b) Retirement Home	Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned
c) Supportive Housing	Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment; may offer physiotherapy and rehabilitation services
d) Long-term Care/Skilled Nursing Facility	Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy, and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital
e) Hospice	Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤ 3 mo

- names of community healthcare institutions, types of facilities, and services offered vary between geographical locations
- factors to consider when referring to community services and institutions: level and type of support required, income/socioeconomic status, social supports and/or degree of social isolation, other social determinants of health creating potential barriers to care

Geriatric Pharmacology

Pharmacokinetics

Table 9. Age-Associated Pharmacokinetics

Parameter	Age Effect	Implications
Absorption (less significant)	Increased gastric pH, decreased splanchnic blood flow, GI absorptive surface and dermal vascularity, delayed gastric emptying. However, appropriate absorption of most oral drugs is seen in healthy older-aged patients except for drugs with extensive first pass metabolism; reduced absorption may be related to patient comorbidities	Comorbidities, drug-drug, and drug-food interactions are more likely to affect absorption
Distribution	Increased total body fat Decreased lean body mass and total body water Increased α1-glycoprotein Decreased albumin	Lipophilic drugs have a larger volume of distribution Decreased volume of distribution of hydrophilic drugs Increased binding of basic drugs Decreased binding of acidic drugs
Metabolism (aging effect less significant)	Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)	Lower doses may be therapeutic
Elimination	Decreased renal blood flow, glomerular filtration rate, tubular secretion Overall reduction in renal function by 30-50%	Lower doses may be therapeutic

Pharmacodynamics

Drug Sensitivity
- changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives, antipsychotics, anticholinergics, digoxin, and narcotics
- decreased sensitivity to β-blockers and β-adrenergic stimulants, though may have increased sensitivity

Decreased Homeostasis
- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

Polypharmacy

Definition
- prescription, administration, or use of more medications than are clinically indicated

Epidemiology
- in Canada, >60% of older adults reported using ≥5 medications
- hospitalized older adults are given an average of 10 medications during admission

Risk Factors for Polypharmacy
- patient-level risk factors: age, female sex, cognitive impairment, low health literacy, frailty, mental health conditions, multiple chronic conditions, lack of primary care physician, residing in LTC, multiple pharmacies
- systems-level risk factors: multiple prescribers, poor documentation systems, automated refill systems, lack of systematic medication review

Risk Factors for Non-Compliance
- greater number of medications (compliance with 1 medication is 80%, but drops to 25% with ≥6 medications)
- increased dosing frequency, complicated container design, financial constraints, and cognitive impairment

Adverse Drug Reactions (ADRs)
- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in older adults
  - intrinsic: comorbidities (>5), age >85, low BMI, age-related changes in pharmacokinetics and pharmacodynamics, CrCl <50 mL/min
  - extrinsic: number of medications (>9 medications, >12 doses/d), multiple prescribers, unreliable drug history, prior ADR

New medications: Start Low, Go Slow! Avoid starting 2 drugs at the same time.

Adverse drug reactions in older adults may present as delirium, falls, fractures, urinary incontinence/retention, or fecal incontinence/impaction. Any new symptom in older adult could be medication related until proven otherwise.

- prescribing cascade: process whereby an ADR is misinterpreted as a new medical condition, and a subsequent drug is prescribed to treat the initial drug-induced event. Providers should ask themselves:
  - is the new drug being prescribed to address an adverse event from a previously prescribed drug therapy?
  - is the initial drug therapy really needed, especially if leading to a drug cascade?
  - do the benefits of the initial drug therapy outweigh the harms?

Preventing Polypharmacy

- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical comorbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an ADR with another medication

Inappropriate Prescribing in Older Adults

Epidemiology

- the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

Beers Criteria

- a list of medications to avoid in adults ≥65 yr due to safety concerns
- 2019 update lists drugs that are inappropriate in most older adults, those that should typically be avoided with certain conditions, drugs to use with caution, drug-drug interactions, and drug dose adjustment based on kidney function
- examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives

STOPP/START Criteria

- another screening tool for potentially inappropriate prescribing in older adults
- STOPP: Screening Tool of Older Person's Prescriptions
  - systems-based list of medications contraindicated in adults ≥65 yr in the context of their diagnoses
- START: Screening Tool to Alert physicians to Right Treatment
  - systems-based list of medications indicated in adults ≥65 yr in the context of their diagnoses
- older adults are often under-treated (ACEI, ASA, β-blockers, thrombolytics, oral anticoagulants)

Principles for Prescribing in Older Adults

CARED
Caution/Compliance
Age (adjust dosage for age)
Review regimen regularly
Educate
Discontinue unnecessary medications
Geriatric Pearls. Philadelphia: FA Davis Company, 1999

Inappropriate prescribing in older persons: A systematic review of medications available in different criteria
Arch Gerontol Geriatr 2017;68:55-61
Purpose: Comprehensive review of all potentially inappropriate medications for older persons, included in prescribing criteria of the last decade.
Results: From 778 articles, 14 criteria were included in the final analysis, including a total of 729 medication classes among all analyzed criteria. Diazepam was included in all 14 criteria, followed by amitriptyline in 13 criteria and doxepin in 12 criteria. Benzodiazepines, antihistamines, and antipsychotics were the most common drugs reported as potentially inappropriate for older adults, among final criteria.
Conclusion: Benzodiazepines, NSAIDs, antihistamines, and antipsychotics were the most common drugs reported as potentially inappropriate for older persons.

Common Medications

Table 10. Common Medications

Drug Name	Brand Name	Dosing Schedule	Indications	Contraindications	Side Effects	Mechanism of Action
Cognitive Enhancers						
donepezil	Aricept®	5-10 mg PO once daily	Moderate to severe dementia of Alzheimer's type	Known hypersensitivity, caution in untreated obstructive airway disease, cardiac conduction abnormalities, active PUD or occult GI bleed, seizure disorder, syncope NYD	N/V, diarrhea, anorexia, insomnia, fatigue, muscle cramps, syncope, bradycardia (uncommon), heart block (uncommon)	Reversible inhibition of acetylcholinesterase
galantamine	Reminyl®	8-12 mg PO BID	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, caution in untreated obstructive airway disease, cardiac conduction abnormalities, active PUD or occult GI bleed, seizure disorder, syncope NYD	N/V, diarrhea, anorexia, weight loss, headache, dizziness, syncope, heart block (rare), seizure (rare), delirium (rare)	Reversible inhibition of acetylcholinesterase
rivastigmine	Exelon®	1.5 mg PO BID (starting) up to 6-12 mg PO BID	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, severe hepatic disease, caution in untreated obstructive airway disease, cardiac conduction abnormalities, active PUD or occult GI bleed, seizure disorder, syncope NYD	N/V, diarrhea, headache, dizziness, anorexia, insomnia, weight loss, delirium, heart block (rare)	Acetylcholinesterase inhibition (reversible but very slow)
memantine	Ebixa®/Namenda® (Can)/(U.S.)	5 mg PO once daily (starting) up to 10 mg PO BID	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, conditions that alkalinize urine, caution in renal failure, seizures	Dizziness, headache, hypertension, constipation, confusion, hallucinations	NMDA-receptor antagonist
Laxatives						
bran	All-Bran®	1 cup PO once daily	Constipation		Bloating, flatus	Bulk-forming laxative
psyllium	Metamucil® Prodiem® Plain®	3.4 g PO once daily to TID	Constipation, hypercholesterolemia	N/V, abdominal pain, obstruction if another medication is taken within 2 h	Bloating, flatus	Bulk-forming laxative
lactulose	Chronulac® Cephulac® Kristalose®(U.S.) Acilac®; Apo-Lactulose®; Laxilose®; PMS-Lactulose® (Can)	15-30 cc PO once daily/BID and 5-10 mL PO BID for 2-4 wk for bowel evacuation after barium	Constipation, hepatic encephalopathy, bowel evacuation following barium exam	Patients on low galactose diets, abdominal pain, N/V	Flatus, cramps, nausea, diarrhea	Osmotic laxative
PEG 3350 (polyethylene glycol)	Lax-A-Day®, RestoraLAX®, Pegalax® (Can) Gavilax®, Healthylax® (U.S.)	17 g PO once daily (~1 heaping tablespoon) dissolved in 1 cup (250 mL) of beverage	Constipation, bowel prep (different dosing schedule)	Known/suspected bowel obstruction, known hypersensitivity, renal impairment	Abdominal cramps, bloating of the stomach, diarrhea, flatulence, nausea	Osmotic laxative
senna	Senokot®/Ex-lax®	2-4 tablets PO once daily or 10-15 mL syrup once daily/BID. Dosing should be the smallest required to pass soft stool	Constipation	Known/suspected bowel obstruction or abnormal constriction, atonic bowel, IBD, abdominal pain NYD, rectal bleeding NYD, severe dehydration	Abdominal cramps, N/V, diarrhea, urine and/or fecal discolouration	Stimulant laxative
bisacodyl	Dulcolax®	5-15 mg PO (10 mg PR)	Constipation	Acute GI diseases (e.g. appendicitis, diarrhea), ileus, obstruction, abdominal pain, N/V, severe dehydration, and ulcerative proctitis and/or anal fissures if PR	Abdominal cramps, pain, diarrhea, dehydration, dizziness, N/V	Stimulant laxative
Parkinsonian Agents – see Neurology, Table 26, N57						

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in older adults

Landmark Geriatric Medicine Trials

Trial Name	Reference	Clinical Trial Details
FRAILTY		
Gait Speed and Survival in Older Adults, Studenski et al. 2011	JAMA 2011;305:50-58	**Title:** Gait Speed and Survival in Older Adults **Purpose**: Evaluate the relationship between gait speed and survival. **Methods**: Pooled analysis of 9 cohort studies of adults >65 yr with baseline gait speed data, followed up for 6-21 yr. The main outcomes were survival and life expectancy. **Results**: The overall 5-yr survival was 84.8% and 10-yr survival was 59.7%. Gait speed was associated with survival in all studies (pooled hazard ratio per 0.1 m/s, 0.88; 95% CI 0.87 to 0.90; P<0.001). Survival increased across the range of gait speeds with significant increments at 0.1 m/s. **Conclusions**: Gait speed was associated with 10-yr survival in all studies, with considerable variability in predicted 10-yr survival across the range of gait speeds, at 75 yr.
Frailty in Older Adults: Evidence for a Phenotype, Fried et al. 2001	J Gerontol A Biol Sci Med Sci 2001;56(3): M146-56	**Title:** Frailty in Older Adults: Evidence for a Phenotype **Purpose**: Develop phenotype of frailty as a clinical syndrome. **Methods**: Baseline and annual follow-up for outcomes of incident disease, hospitalization, falls, disability, and mortality in an original cohort of 4735 participants and later-recruited cohort of 582 African American participants. All participant data from the prospective observational Cardiovascular Health Study. **Results**: Frailty may be defined as the presence of three or more of: unintentional weight loss (10 lbs in past yr), self-reported exhaustion, weakness (grip strength), slow walking speed, low physical activity. Frailty is associated with increased risk of comorbidity and disability. **Conclusions**: Frailty in community-dwelling older adults may be defined as above. While comorbidity is a risk factor for frailty and disability is an outcome of frailty, frailty itself does not equal comorbidity or disability. Assessment for frailty is vital in identifying patients at increased risk for comorbidity and disability.
REHAB-AF	NEJM 2021;385:203-216	**Title:** Physical Rehabilitation for Older Patients Hospitalized for Heart Failure **Purpose**: Investigate interventions to address physical frailty in older patients hospitalized for acute decompensated heart failure. **Methods**: Multicenter, randomized, controlled trial to evaluate transitional, tailored, progressive rehabilitation intervention, including four physical-function domains initiated during or soon after heart failure hospitalization and continued post-discharge for 36 sessions. Primary outcome was Short Physical Performance Battery score, and secondary outcome was 6 month rehospitalization rate. **Results**: Older adults hospitalized for acute decompensated heart failure produce improved clinical outcomes when treated with this rehabilitation intervention program.
DELIRIUM		
Delirium is a Strong Risk Factor for Dementia in the Oldest-Old: A Population-Based Cohort Study, Davis et al. 2012	Brain 2012;135(9):2809-16	**Title:** Delirium is a Strong Risk Factor for Dementia in the Oldest-Old: A Population-Based Cohort Study **Purpose**: Use a true population sample to determine if delirium is an incident risk factor for incident dementia and cognitive decline. **Methods**: 553 individuals aged >85 yr were used to assess associations between delirium and incident dementia, as well as decline in MMSE scores. The relationship between dementia common neuropathological markers was modelled and stratified. **Results**: Delirium increased the risk of incident dementia (OR 8.7; 95% CI 2.1 to 35), worsened dementia severity (OR 3.1; 95% CI 1.5 to 6.3) and deterioration in global function score (OR 2.8; 95% CI 1.4 to 5.5). Delirium was associated with a loss of 1.0 more MMSE points per yr (95% CI 0.11 to 1.89) than those with no history of delirium. **Conclusions**: Delirium is a strong risk factor for incident dementia and cognitive decline in elderly patients
A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients, Inouye et al. 1999	NEJM 1999;340:669-676	**Title:** A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients **Purpose**: Evaluate the effectiveness of a multicomponent strategy for delirium prevention among older inpatients. **Methods**: A total of 852 inpatients ≥70 yr were included in the study. In lieu of randomization, prospective individual matching was used to compare patients admitted to an intervention unit vs. one of two usual care units. In the intervention unit, the multicomponent approach sought to address cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. **Results**: Delirium developed in 9.9% of patients in the intervention unit, vs. 15% in the usual care unit (95% CI 0.39 to 0.92). Total number of days with delirium (105 d vs. 161 d, P=0.02) and total number of delirium episodes (62 vs. 90, P=0.03) were both lower in the intervention unit. **Conclusions**: A multicomponent intervention model aimed at addressing risk factors for delirium in hospitalized older adults is effective at reducing delirium incidence and delirium duration.
FALLS		
PROFET	Lancet 1999;353:93-97	**Title:** Prevention of Falls in the Elderly Trial (Profet): A Randomised Controlled Trial **Purpose**: Assess the benefit of a structured interdisciplinary assessment of people who have fallen. **Methods**: Patients >65 yr presenting to ED with a fall were randomized to the intervention group (detailed medical and OT-therapy assessment with referral if indicated) or to a control group (usual care only). **Results**: The risk of falling was significantly lower in the intervention group compared to the control group (OR 0.39; 95% CI 0.23 to 0.66) as was the risk of fall recurrence (OR 0.33; 95% CI 0.16 to 0.68). **Conclusions**: Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment.
NEUROCOGNITIVE DISORDERS		
Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease, Howard et al. 2012	NEJM 2012;366:893-903	**Title:** Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease **Purpose**: Assess the benefits of cholinesterase inhibitors for the long-term treatment of moderate-severe Alzheimer's disease. **Methods**: 295 community-dwelling patients with moderate-severe Alzheimer's disease treated with donepezil were randomized to either continue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. The primary outcomes were SMMSE scores and Bristol Activities of Daily Living (BADLS) scores. **Results**: Patients assigned to continue donepezil, compared to those who discontinued, had a 1.9 higher average SMMSE score (95% CI 1.3 to 2.5). The score on the BADLS was lower (less impairment) by 3.0 points (95% CI 1.8 to 4.3) (P<0.001 for both comparisons). Patients who received memantine, compared with placebo, had a 1.2 higher average SMMSE score (95% CI 0.6 to 1.8, P <0.001) and BADLS score that was 1.5 points lower (95% CI 0.3 to 2.8; P=0.02). **Conclusions**: Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer's disease.

Trial Name	Reference	Clinical Trial Details
HYPERTENSION IN THE ELDERLY		
Syst-Eur	Lancet 1997;350:757-64	**Title:** Randomised Double-blind Comparison of Placebo and Active Treatment for Older Patients with Isolated Systolic Hypertension. The Systolic Hypertension in Europe (Syst-eur) Trial Investigators **Purpose**: Investigate whether active treatment could reduce CV complications of isolated systolic HTN. **Methods**: Patients >60 yr were randomly assigned to nitrendipine 10-40 mg daily with the possible addition of enalapril 5-20 mg daily and hydrochlorothiazide 12.5-25 mg daily, or to matching placebos. Combined fatal and nonfatal stroke was the primary endpoint. **Results**: Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1000 patient-years (43% reduction; P=0.003). Nonfatal stroke reduced by 44% (P=0.007) and nonfatal cardiac endpoints decreased by 33% (P=0.03). All-cause mortality was not influenced. **Conclusions**: Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications.
HYVET	NEJM 2008;358:1887-98	**Title:** Treatment of Hypertension in Patients 80 Years of Age or Older **Purpose**: Determine whether treatment of hypertension is beneficial in patients >80 yr. **Methods**: 3845 patients >80 yr and a sustained sBP >160 mmHg were randomized to receive indapamide SR 1.5 mg or matching placebo. The ACEI perindopril 2 or 4 mg was added if necessary, to achieve the target BP of 150/80 mmHg. The primary endpoint was fatal or nonfatal stroke. **Results**: The mean BP at 2 yr was 15.0/6.1 mmHg lower in the active-treatment group than in the placebo group. Active treatment was associated with a 30% reduction in the rate of death from stroke (95% CI 1 to 62; P=0.05), a 21% reduction in all-cause mortality (95% CI; 4 to 35; P=0.02). Fewer adverse events were reported in the active-treatment group. **Conclusions**: Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in adults >80 yr is beneficial.
INAPPROPRIATE PRESCRIBING IN THE ELDERLY		
EMPOWER	JAMA Intern Med 2014;174:890-98	**Title:** Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education: The Empower Cluster Randomized Trial **Purpose**: Compare the effect of direct-to-consumer education against usual care on benzodiazepine discontinuation in older adults. **Methods**: 303 long-term users of benzodiazepines aged 65-95 were randomized to the educational intervention (deprescribing patient empowerment intervention explaining risks of benzodiazepine use and a stepwise taper protocol) or the 'wait list' control. Primary outcomes were benzodiazepine discontinuation after 6 mo. **Results**: At 6 mo, 27% of patients in the intervention group had discontinued benzodiazepines, compared with 5% in the control group (risk difference 23%; 95% CI 14% to 32%). **Conclusions**: Direct-to-consumer education describing the risks of benzodiazepine use and a stepwise tapering protocol effectively elicits shared decision making and discontinuation of medications that increase the risk of harm in older adults.
STOPP and START	Int J Clin Pharmacol Ther 2008;46:72-83	**Title:** STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation **Purpose**: Validate a new screening tool of older persons' prescriptions, incorporating criteria for potentially inaccurate prescriptions (called STOPP), and criteria for appropriate prescriptions (called START). **Methods**: A Delphi consensus technique was used to obtain validity from an 18-member expert panel. Inter-rater reliability was assessed by determining the kappa-statistic on 100 datasets. **Results**: STOPP consists of 65 clinically significant criteria for potentially inappropriate prescriptions; START consists of 22 evidence-based prescribing indicators. **Conclusions**: STOPP/START is a valid, reliable, and comprehensive screening tool that enables the prescribing physician to appraise an older patient's prescription drugs in the context of his/her concurrent diagnoses.

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GY Gynecology

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Acronyms

ACEI	angiotensin converting enzyme inhibitors	GA	gestational age	IVM	in vitro maturation		quantification
AFP	α-fetoprotein	GIFT	gamete intrafallopian transfer	JRA	juvenile rheumatoid arthritis	PV	per the vagina administration
AIS	androgen insensitivity syndrome	GnRH	gonadotropin-releasing hormone	LEEP	loop electrosurgical excision procedure	RPR	rapid plasma reagin
AMH	anti-müllerian hormone	GTD	gestational trophoblastic disease	LHRH	luteinizing hormone-releasing hormone	RR	risk ratio
ARB	angiotensin II receptor blockers	GTN	gestational trophoblastic neoplasia	LMP	last menstrual period	SCC	squamous cell carcinoma
ASCUS	atypical squamous cells of undetermined significance	HERS	heart and estrogen/progestin replacement study	LN	lymph node	SERM	selective estrogen receptor modulator
AUB	abnormal uterine bleeding	HMG	human menopausal gonadotropin	LNMP	last normal menstrual period	SHBG	sex hormone binding globulin
BMD	bone mineral density	HPO	hypothalamic-pituitary-ovarian	LSIL	low grade squamous intraepithelial lesion	SHG	sonohysterography
BSO	bilateral salpingo-oophorectomy	HPV	human papillomavirus	LVSI	lymphovascular space involvement	SPRM	selective progesterone receptor modulator
BUC	buccal administration	HRT	hormone replacement therapy	MHT	menopause hormone therapy	SSRIs	selective serotonin reuptake inhibitor
BV	bacterial vaginosis	HSG	hysterosalpingography	MRKH	Mayer-Rokitansky-Küster-Hauser	TAH	total abdominal hysterectomy
CA-125	cancer antigen 125	HSIL	high grade squamous intraepithelial lesion	MTX	methotrexate	TET	tubal embryo transfer
CAH	congenital adrenal hyperplasia	HSV	herpes simplex virus	NK	natural killer	TH	total hysterectomy
CHC	combined hormonal contraception	IBD	inflammatory bowel disease	OCP	oral contraceptive pill	TOT	tension-free transobturator tape
CMV	cytomegalovirus	ICSI	intracytoplasmic sperm injection	OGTT	oral glucose tolerance test	TVT	tension-free vaginal tape
CRP	C-reactive protein	ITP	immune thrombocytopenic purpura	PCOS	polycystic ovarian syndrome	TZ	transformation zone
DES	diethylstilbestrol	IUD	intrauterine device	PG	prostaglandin	UAE	uterine artery embolization
DHEA	dehydroepiandrosterone	IUI	intrauterine insemination	PID	pelvic inflammatory disease	VIN	vulvar intraepithelial neoplasia
DMPA	depot medroxyprogesterone acetate or Depo-Provera®	IUS	intrauterine system	PMB	postmenopausal bleeding	VTE	venous thromboembolism
DUB	dysfunctional uterine bleeding	IVDU	intravenous drug use	PMDD	premenstrual dysphoric disorder	VWD	von Willebrand disease
DVT	deep venous thrombosis	IVF	in vitro fertilization	PMN	polymorphonuclear neutrophils	W/D	withdrawal
EPC	emergency postcoital contraception			PMS	premenstrual syndrome	WHI	Women's Health Initiative
ESR	erythrocyte sedimentation rate			POP-Q	pelvic organ prolapse	ZIFT	zygote intrafallopian transfer

Basic Anatomy Review

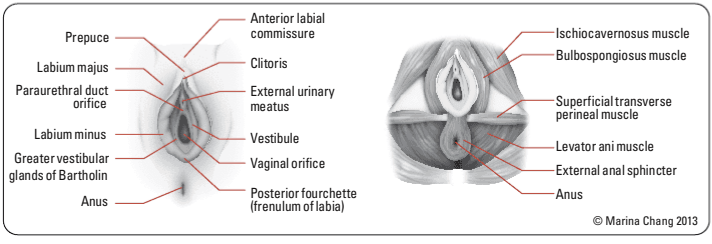


Figure 1. Vulva and perineum

A. External Genitalia

- blood supply: internal pudendal artery, superficial external pudendal artery (labia majora)
- sensory innervation: pudendal nerve
- lymphatic drainage: superficial inguinal lymph nodes, deep inguinal lymph nodes (clitoris)

B. Vagina

- muscular canal extending from cervix to vulva, anterior to rectum, and posterior to bladder
- lined by rugated, stratified squamous epithelium
- upper vagina separated by cervix into anterior, posterior, and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastomoses from uterine, inferior vesical, and middle rectal arteries

C. Uterus

- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterine corpus, made up of the isthmus, fundus, and body
    - blood supply: uterine artery (branch of the internal iliac artery, anterior division)
  - cervix
    - blood supply: cervical branch of uterine artery
- supported by the pelvic diaphragm, the pelvic organs, and four paired sets of ligaments
  - round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals (canal of Nuck), then terminate in the labia major
    - function: anteversion/suspension
    - blood supply: Sampson's artery (branch of uterine artery running through round ligament)
  - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
    - function: mechanical support for uterus, prevent prolapse, and contain autonomic nerve fibres

- cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
  - function: mechanical support, prevent prolapse
- broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics. Within the broad ligament, the uterine artery anastomoses with the ovarian artery

- infundibulopelvic ligament (suspensory ligament of the ovary): continuous tissue that connects ovary to pelvic wall
  - contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
- position of the uterus
  - **anteverted** (majority), retroverted, neutral
  - **anteflexed** (more common), retroflexed

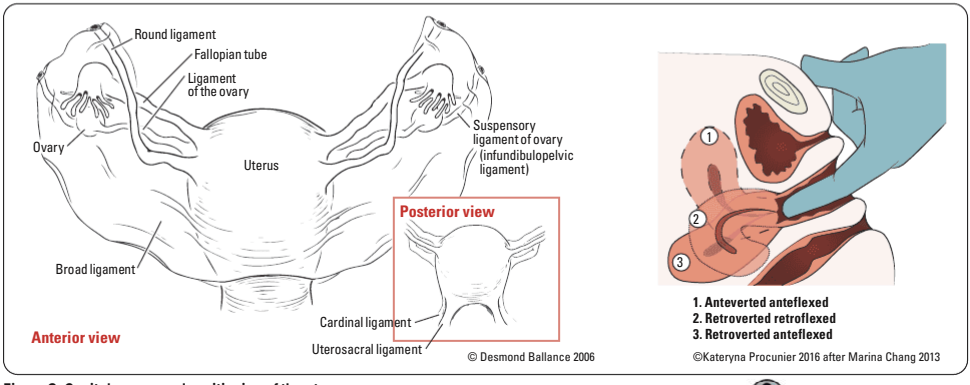


Figure 2. Genital organs and positioning of the uterus

D. Fallopian Tubes

- 8-14 cm muscular tubes extending laterally from the uterus to the ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

E. Ovaries

- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off of aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

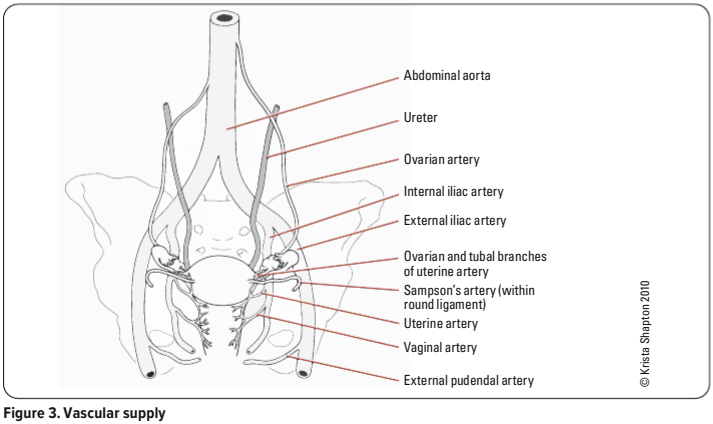


Figure 3. Vascular supply

Determination of Uterine Position by Clinical Exam

- If cervix faces anteriorly (under the urethra/pubic symphysis and less easily accessible), i.e. toward bladder more likely **RETROVERTED UTERUS**
- If cervix faces posteriorly (easily accessible), i.e. toward sacrum or rectum, more likely **ANTEVERTED UTERUS**
- If uterus is palpable with the abdominal hand on bimanual exam, more likely **ANTEVERTED UTERUS**
- If uterus is palpable behind the cervix in the posterior fornix, more likely **RETROVERTED UTERUS**

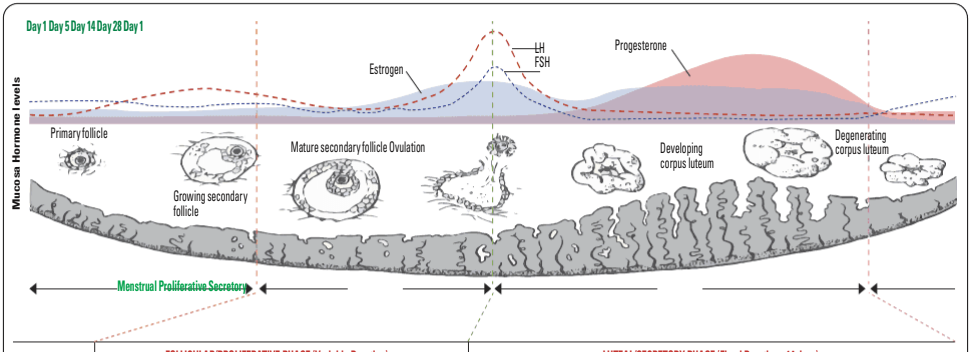
"Water Under the Bridge"
The ureters run inferior to the uterine arteries

Common Anatomy Questions in the OR

What is the origin of the left and right ovarian arteries?
Descending aorta
What are the drainage sites for the left and right ovarian veins?
Left to left renal vein, right to inferior vena cava
What is the most common place to locate the ureter?
In the pelvic brim, the ureter passes over the iliac vessels. The ureter can also be found in the medial leaf of the broad ligament where the ureter passes under the uterine artery
Which artery runs through the round ligament?
Sampson's artery

Menstruation

Menstrual Cycle



	FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)			LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)		
	Early	Mid	Late	OVULATION	Early-Mid	Late
Initiating Events	↓ E and ↓ P (from end of previous cycle)	↑ FSH acts on ovarian granulosa cells	Growing follicles continue to secrete E	Sudden switch from negative to positive feedback (E and P now ↑ FSH & LH)	Switch back to negative feedback	No fertilized oocyte
HPO Axis	↑ GnRH pulse frequency ↑ FSH ↑ LH pulse frequency	↑ E from follicles (ovary)		↑↑ LH pulse amplitude (LH surge)	↓ LH	
Hormones			↑ E from follicles, especially from dominant follicle	E peaks → LH surge → ovulation	↑ P from corpus luteum	↓ P secondary to degeneration of corpus luteum
Feedback on HPO Axis		Negative feedback E → ↓ FSH, ↓ LH		Positive feedback: E and P → ↑ FSH, ↑ LH	Negative feedback: P → ↓ FSH, ↓ LH	
Ovaries	↑ FSH → follicular growth in 3-30 follicles	↑ follicular growth (by reducing atresia) → ↑ E	Dominant follicle persists, remainder undergo atresia Granulosa cells luteinize → produce P	~36 h after LH surge, dominant follicle releases oocyte; corpus luteum (remnant of dominant follicle) produces P		Cessation of P from corpus luteum
Endometrium	Menses from P withdrawal (from end of previous cycle)				P stabilizes endometrium	Withdrawal of P → menses
Cervical Mucus		Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy				Cervical mucus: Opaque, scant amount, Spinnbarkeit 1-2 cm

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CHARACTERISTICS
- Menarche 10-15 yr
- Average 12.2 yr
- Entire cycle 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

ESTROGEN
ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle

Estrogen effects
- On the follicles in the ovaries: reduces atresia
- On the endometrium: proliferation of glandular and stromal tissue
- On all target tissues: decreases estrogen receptors

PROGESTERONE
PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle)

Progesterone effects
- On the endometrium: cessation of mitoses (stops building endometrium up), "organization" of glands (initiates secretions from glands), inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues: decrease estrogen receptors (the "anti-estrogen" effect), decrease progesterone receptors

Figure 4. Events of the normal menstrual cycle
E = estrogen; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; HPO = hypothalamic-pituitary-ovarian; LH = luteinizing hormone; P = progesterone

Stages of Puberty

- see Pediatrics, P7
- adrenarche: increased secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8 yr
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding

Stages of Puberty

"Boobs, Pubes, Grow, Flow"
Thelarche, Pubarche, Growth spurt, Menarche

Premenstrual Syndrome

Definition
- physiological and emotional disturbances that occur 1-2 wk prior to menses and last until a few days after onset of menses; common symptoms include depression, irritability, tearfulness, and mood swings
- synonyms: "ovarian cycle syndrome," "menstrual molimina" (moodiness)

Etiology
- multifactorial: not completely understood; genetics likely play a role
- CNS-mediated neurotransmitter (serotonin, dopamine, GABA) interactions with sex steroids (progesterone, estrogen, and testosterone)
- serotonergic dysregulation – currently most plausible theory

Diagnostic Criteria for Premenstrual Syndrome
- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness or swelling, abdominal bloating, headache, swelling of extremities, joint or muscle pain, weight gain, fatigue
- symptoms relieved within 4 d of onset of menses and do not recur until at least day 13 of cycle
- symptoms present in the absence of any pharmacologic therapy, hormone ingestion, drug, or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or occupational performance
- consider a PRISM (Prospective Record of the Impact and Severity of Menstrual symptoms) calendar to monitor symptoms and confirm diagnosis particularly with 3rd line treatment

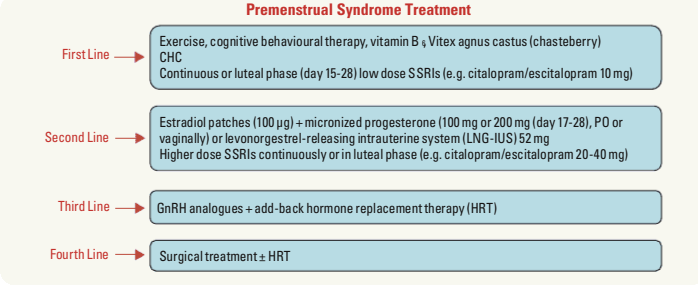

Premenstrual Syndrome Treatment
First Line
Exercise, cognitive behavioural therapy, vitamin B 6 Vitex agnus castus (chasteberry)
CHC
Continuous or luteal phase (day 15-28) low dose SSRIs (e.g. citalopram/escitalopram 10 mg)
Second Line
Estradiol patches (100 µg) + micronized progesterone (100 mg or 200 mg (day 17-28), PO or vaginally) or levonorgestrel-releasing intrauterine system (LNG-IUS) 52 mg
Higher dose SSRIs continuously or in luteal phase (e.g. citalopram/escitalopram 20-40 mg)
Third Line
GnRH analogues + add-back hormone replacement therapy (HRT)
Fourth Line
Surgical treatment ± HRT

Figure 5. Royal College of Obstetricians and Gynecologists (RCOG) guidelines for treatment of premenstrual syndrome
Adapted from source: Management of Premenstrual Syndrome. Brit J Obstet Gynec 2016;48:1-33

Tanner Stage

Thelarche
1. None
2. Breast bud
3. Further enlargement of areolae and breasts with no separation of contours
4. 2° mound of areolae and papilla
5. Areolae recessed to general contour of breast

Pubarche
1. None
2. Downy hair along labia only
3. Darker/coarse hair extends over pubis
4. Adult-type hair with no thigh involvement
5. Adult hair in distribution and type, extends over thighs. Not all patients achieve Tanner Stage 5. For image see Pediatrics, P38

Premenstrual Dysphoric Disorder

Definition
- PMDD is similar to PMS but causes more severe symptoms and impairment of functioning

Clinical Features
- irritability and depressed mood
- breast pain and abdominal bloating

Diagnostic Criteria for Premenstrual Dysphoric Disorder
- at least 5 of the following 11 symptoms during most menstrual cycles of the last year (with at least 1 of the first 4)
  - depressed mood or hopelessness
  - anxiety or tension
  - affective instability

  - anger or irritability
  - decreased interest in activities
  - difficulty concentrating
  - lethargy
  - change in appetite
  - hypersomnia or insomnia
  - feeling overwhelmed
  - physical symptoms: breast tenderness/swelling, headaches, joint/muscle pain, bloating, or weight gain
- symptoms cause significant distress and/or interfere with social or occupational functioning
- symptoms must be present during the week prior to menses and resolve within a few days after onset of menses
- may be superimposed on other psychiatric disorders, provided it is not merely an exacerbation of another disorder

Common Investigations and Procedures

Imaging

Ultrasound

- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if β-hCG ≥1500 (β-hCG must be ≥6500 for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, and ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterise fibroids
  - detection of deep infiltrating endometriosis
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal patients

Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
- pre-treatment with misoprostol (Cytotec®) is optional (less effective in postmenopause)
- more invasive procedure (i.e. D&C) may be done in the office or operating room ± hysteroscopy (this may be required if endometrial biopsy is not possible in the office setting or if there is suspicion for an endometrial polyp/intrauterine pathology or other risk factors for endometrial hyperplasia/cancer)
- detection rate of >97% for endometrial biopsy
- indications
  - AUB/PMB
    - age >40
    - risk factors for or history of endometrial cancer
    - failure of medical treatment
    - significant intermenstrual bleeding
    - consider in patients with infrequent menses suggesting anovulatory cycles
    - obesity

Hysterectomy

Indications

- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications

- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)
- venous thromboembolism

No. 377 – Recommendations for Hysterectomy for Benign Gynaecological Indications in the SOGC Clinical Practice Guidelines
J Obs Gyn Can 2019; 41(4): 543-557
Summary:
1. Hysterectomy should be approached by either vaginal, laparoscopic, or open routes.
2. Correction of preoperative anemia (Hb <120 g/L), preoperative antibiotic prophylaxis, and measures to decrease risk of venous thromboembolism are recommended.
3. In patients with endometriosis, full excision of local endometriosis should be performed concurrently.
4. Opportunistic salpingectomy can be considered at the time of hysterectomy, but the planned surgical approach should not be changed for this sole purpose.
5. Urinary tract injury is a known complication of hysterectomy and there should be a low threshold for further investigation in cases where injury is suspected – consider routine cystoscopy.
6. Patients should be counseled about the benefits and risks of removing the ovaries, the risk of ovarian cancer vs. the long-term health implications of earlier menopause.

Approaches (www.tvasurg.com)

1. open (abdominal approach): uterus removed via transverse (Pfannenstiel, Maylard) or midline laparotomy
2. minimally invasive approaches
   - vaginal hysterectomy: entire procedure performed through the vagina; no abdominal incisions
   - laparoscopic-assisted vaginal hysterectomy: vascular pedicles are divided by a combination of laparoscopic and vaginal approaches
   - total laparoscopic hysterectomy: all vascular pedicles including the colpotomy approached laparoscopically and removed through the vagina or a mini-laparotomy
   - robotic: a type of laparoscopic approach; may be advantageous in patients with a high BMI, but more costly

Table 1. Classification of Hysterectomy

Classification	Tissues Removed	Indications
Subtotal Hysterectomy	Uterus	Inaccessible cervix (e.g. adhesions) Patient choice/preference
Total Hysterectomy (TH) (extrafascial simple hysterectomy/type 1) ± Bilateral Salpingectomy	Uterus, cervix, uterine artery ligated at uterus ± fallopian tubes	Uterine fibroids Endometriosis Adenomyosis Heavy menstrual bleeding DUB Tubes often removed opportunistically if already doing hysterectomy
Total Hysterectomy (TH) (extrafascial simple hysterectomy/type 1) and Bilateral Salpingo-Oophorectomy (BSO)	Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries	Endometrial cancer Malignant adnexal masses Consider for endometriosis Any indication for hysterectomy in a postmenopausal patient
Modified Radical Hysterectomy (type 2)	Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, midpoint of uterosacral ligaments, and upper 1-2 cm vagina	Cervical cancer (up to stage 1B1)
Radical Hysterectomy (type 3)	Uterus, cervix, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum), and upper 1/3-1/2 vagina	Cervical cancer

Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

With Secondary Sexual Development		Without Secondary Sexual Development	
Normal Breast and Pelvic Development	**Normal Breast, Abnormal Uterine Development**	**High FSH (Hypergonadotropic Hypogonadism)**	**Low FSH (Hypogonadotropic Hypogonadism)**
Hypothyroidism Hyperprolactinemia PCOS Hypothalamic dysfunction	Androgen insensitivity Anatomic abnormalities Müllerian agenesis, uterovaginal septum, imperforate hymen	Gonadal dysgenesis Abnormal sex chromosomes (Turner's XO) Normal sex chromosomes (46XX, 46XY)	Constitutional delay (rare in girls) Congenital abnormalities Isolated GnRH deficiency Pituitary failure (Kallmann syndrome, head injury, pituitary adenoma, etc.) Acquired endocrine disorders (type 1 DM) Pituitary tumours Systemic disorders (IBD, JRA, chronic infections, etc.) Functional hypothalamic amenorrhea Asherman's Syndrome/uterine defect

Primary Amenorrhea
No menses by age 13 in absence of 2° sexual characteristics, or no menses by age 15 with 2° sexual characteristics, or no menses 2 yr after thelarche

Secondary Amenorrhea
No menses for >6 mo or 3 cycles after documented menarche

Most Common Causes of Primary Amenorrhea
1. Gonadal dysgenesis (e.g. Turner's Syndrome)
2. Functional hypothalamic amenorrhea
3. Mullerian agenesis

Table 3. Differential Diagnosis of Secondary Amenorrhea

With Hyperandrogenism	Without Hyperandrogenism
PCOS Autonomous hyperandrogenism (androgen secretion independent of the HPO axis) Ovarian: tumour, hyperthecosis Adrenal androgen-secreting tumour Late onset or mild congenital adrenal hyperplasia (rare)	Pregnancy Hypergonadotropic hypogonadism (i.e. primary ovarian insufficiency: high FSH, low estradiol) Idiopathic Autoimmune: type 1 DM, autoimmune thyroid disease, Addison's disease, celiac disease Iatrogenic: cyclophosphamide drugs, radiation Hyperprolactinemia Endocrinopathies: most commonly hyper or hypothyroidism Hypogonadotropic hypogonadism (low FSH): Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan's syndrome Functional hypothalamic amenorrhea (often related to stress, excessive exercise and/or anorexia)

Functional hypothalamic amenorrhea is the most common cause of secondary amenorrhea

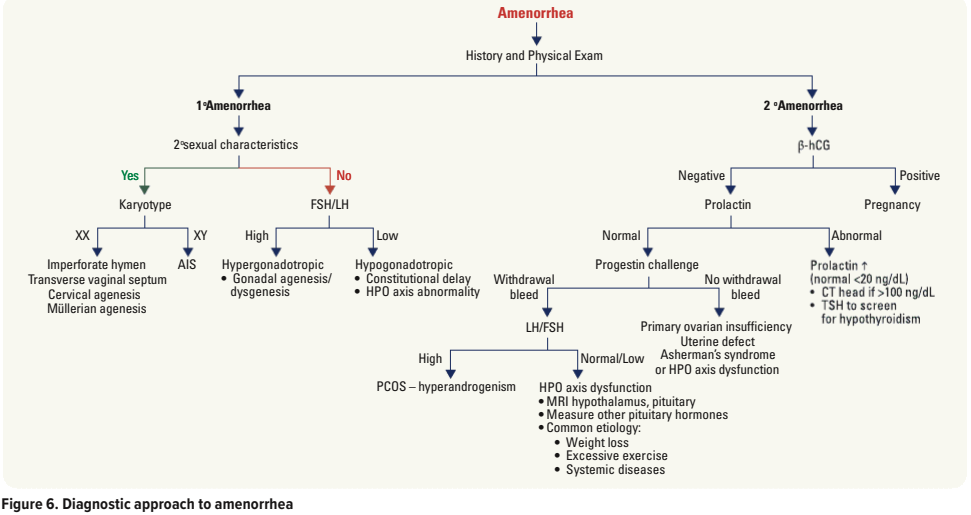


Figure 6. Diagnostic approach to amenorrhea

Investigations

- β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
  - medroxyprogesterone acetate (Provera®) 10 mg PO once daily for 10-14 d
  - any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive W/D test
    - W/D bleed suggests presence of adequate estrogen to thicken the endometrium; thus W/D of progesterone results in bleeding
    - if no bleeding occurs, this may be secondary to inadequate estrogen (hypoestrogenism), excessive androgens or progesterones (decidualization), pregnancy, obstructive causes (e.g. cervical stenosis), or structural causes (e.g. uterine adhesions)
- karyotype: indicated if primary ovarian insufficiency or absent puberty
- U/S to confirm normal anatomy, identify PCOS (in adult population only)

Prolactinoma Symptoms
Galactorrhea, visual changes, headache

Treatment

Table 4. Management of Amenorrhea

Etiology	Management
1° AMENORRHEA	
AIS	Gonadal resection after puberty
	Psychological counselling
	Creation of neo-vagina with dilation
Anatomical	
Imperforate hymen	Surgical management
Transverse vaginal septum	Surgical management
Cervical agenesis	Suppression and ultimately hysterectomy
Müllerian dysgenesis (MRKH syndrome)	Psychological counselling
	Creation of neo-vagina with dilation
	Diagnostic study to confirm normal urinary system and spine
2° AMENORRHEA	
HPO axis dysfunction	Identify modifiable underlying cause
	Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development (NOT proven to work) Correct the problem (weight)
Hyperprolactinemia	MRI/CT head to rule out lesion
	If no demonstrable lesions by MRI:
	Bromocriptine, cabergoline if fertility desired
	Combined OCPs if no fertility desired
	Demonstrable lesions by MRI: surgical management
Polycystic ovarian syndrome	See *Polycystic Ovarian Syndrome, GY25*
Premature ovarian failure	Screen for DM, hypothyroidism, hypoparathyroidism, hypocortisolism
	Hormonal therapy with estrogen and progestin to decrease risk of osteoporosis; can use OCP after induction of puberty
Uterine defect	Evaluation with hysterosalpingography or sonohysterography
Asherman's syndrome	Hysteroscopy: excision of synechiae

2° amenorrhea is pregnancy until proven otherwise

Abnormal Uterine Bleeding

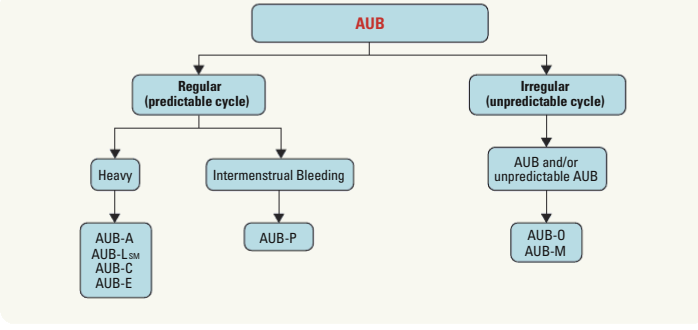


Figure 7. Diagnostic approach to abnormal uterine bleeding

The most common cause of postmenopausal bleeding is genitourinary syndrome of menopause (atrophy). However, endometrial cancer and hyperplasia must be ruled out with an endometrial biopsy before treatment for genitourinary syndrome of menopause (atrophy). 10% of post menstrual bleeding is endometrial cancer.

Approach

- menstrual bleeding should be evaluated by ascertaining: frequency/regularity of menses, duration, volume of flow, impact on quality of life, and timing (inter- or premenstrual, or breakthrough)
- is it regular?
  - regular: cycle to cycle variability of <20 d – "Can you predict your menses within 20 days?"
  - irregular: cycle to cycle variability of ≥20 d
- is it heavy?
  - questions: How frequently do pads/tampons need to be changed? How saturated? Any clots?
  - ≥80 cc of blood loss per cycle or
  - ≥8 d of bleeding per cycle or
  - bleeding that significantly affects quality of life

Abnormal Uterine Bleeding
Change in frequency, duration, or amount of menstrual flow that affects quality of life.

- is it structural?
  - PALM (see *Table 5*)
- is it non-structural?
  - COEIN (see *Table 5*)

Table 5. Abnormal Uterine Bleeding – Etiologies, Investigations, and Management

Etiology	Investigations	Management
	STRUCTURAL	
Polyps (AUB-P)	Transvaginal sonography Saline infusion sonohysterography	Polypectomy (triage based on symptoms, polyp size, histopathology, and patient age)
Adenomyosis (AUB-A)	Transvaginal sonography MRI	See *Adenomyosis, GY13*
Leiomyoma (AUB-L) Submucosal (AUB-Lsm) Other (AUB-Lo)	Transvaginal sonography Saline infusion sonohysterography Diagnostic hysteroscopy MRI	See *Fibroids, GY14*
Malignancy and Hyperplasia (AUB-M)	Transvaginal sonography Endometrial biopsy for all patients >40 yr with AUB, for patients <40 yr with persistent AUB, or endometrial cancer risk factors	Dependent on diagnosis
	NON-STRUCTURAL	
Coagulopathy (AUB-C)	CBC, coagulation profile (especially in adolescents), VWF, Ristocetin cofactor, factor VII	Dependent on diagnosis (hormonal modulation (e.g. OCP), Mirena IUS, endometrial ablation)
Ovulatory Dysfunction (AUB-O)	Bloodwork: β-hCG, ferritin, prolactin, FSH, LH, serum androgens (free testosterone, DHEA, androstenedione), progesterone, 17-hydroxy progesterone, TSH, free T4 Pelvic ultrasound	See *Infertility, GY23*
Endometrial (AUB-E)	Endometrial biopsy	Tranexamic acid Hormonal modulation (e.g. OCP) Mirena IUS Endometrial ablation
Iatrogenic (AUB-I)	Transvaginal sonography (rule out forgotten IUD) Review OCP/HRT use Review medications (especially neuroleptic use)	Remove offending agent
Not Yet Classified (AUB-N)	–	–

Treatment

- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider AUB
- medical
  - mild AUB
    - NSAIDs
    - anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
    - combined hormonal contraceptive
    - progestins (Provera®) on first 10-14 d of each month or every 3 mo if AUB-O
    - Mirena® IUD
    - correct anemia - iron
  - acute, severe AUB
    - replace fluid losses, consider admission
      a) anti-fibrinolytic (e.g. Cyklokapron®) 500-1000 mg PO BID-TID prn (up to 4 g/d)
      b) anti-fibrinolytic (e.g. Cyklokapron®) 10 mg/kg IV q8 h and/or estrogen (Premarin®) 25 mg IV q4 h x 24 h with Gravol® 50 mg IV/PO q4 h (rarely used)
      c) tapering OCP regimen, 35 µg pill (often Marvelon) TID x 7 d then taper to 1 pill/d for 3 wk with Gravol® 50 µg IV/PO q4 h
      d) tapering OCP to 1 tab TID x 2 d → BID x 2 d → once daily (more commonly used) after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
      (e) medical (can also consider):
        – high dose progestins
        – GnRH agonists (e.g. Lupron®) with add-back Norlutate if taken for >6 mo
        – progesterone IUD (Mirena)
        – danazol (Danocrine®)
- surgical
  - polypectomy
  - myomectomy
  - uterine artery embolization
    - if finished childbearing
  - endometrial ablation
    - if finished childbearing
  - repeat procedure may be required if symptoms recur, especially if <40 yr
    - hysterectomy: definitive treatment

Dysmenorrhea

Etiology

- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - PID
  - IUD (copper)
  - uterine polyps
  - foreign body

Primary Dysmenorrhea
Recurrent, crampy lower abdominal pain during menses in the absence of demonstrable disease

Secondary Dysmenorrhea
Pain during menses that can be attributed to an underlying disorder (i.e. endometriosis, adenomyosis, fibroids)

Table 6. Comparison of Primary and Secondary Dysmenorrhea

	Primary Dysmenorrhea	Secondary Dysmenorrhea
Features	Recurrent, crampy lower abdominal pain that occurs during menses in the absence of demonstrable disease	Similar features as primary dysmenorrhea but with an underlying disorder that can account for the symptoms, such as endometriosis, adenomyosis, or uterine fibroids
Signs and Symptoms	Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated)	Same symptoms as primary dysmenorrhea Associated symptoms: dyspareunia, abnormal bleeding, infertility
Diagnosis	Assess for associated dyspareunia, abnormal bleeding, infertility (signs of 2° dysmenorrhea) Rule out underlying pelvic pathology and confirm cyclic nature of pain Pelvic examination not required; indicated for patients not responding to therapy or with signs of organic pathology	Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in patients <20 yr) U/S, laparoscopy, and hysteroscopy may be necessary to establish the diagnosis Vaginal and cervical cultures may be required
Treatment	Regular exercise, local heat NSAIDs: should be started before onset of pain CHCs with continuous or extended use: suppress ovulation/reduce menstrual flow	Treat underlying cause

Endometriosis

Definition

- the presence of endometrial tissue (glands and stroma) outside of the uterine cavity
- chronic condition, resolving only with menopause

Etiology

- not fully understood; proposed mechanisms include (combination likely involved):
  - retrograde menstruation (Sampson's theory)
  - immunologic: decreased NK cell activity limiting clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
  - extra-pelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

Differential Diagnoses
- Chronic PID, recurrent acute salpingitis
- Hemorrhagic corpus luteum
- Benign/malignant ovarian neoplasm
- Ectopic pregnancy

Epidemiology

- incidence: 15-30% of premenopausal patients
- mean age at presentation: 25-30 yr
- regresses after menopause

4 "Dys" of Endometriosis
- Dysmenorrhea
- Dyspareunia (cul-de-sac, uterosacral ligament)
- Dyschezia (uterosacral ligament, cul-de-sac, rectosigmoid attachment)
- Dysuria (bladder involvement)

Risk Factors

- family history (7-10x increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – usually resolves with treatment of anomaly which relates to retrograde menses mechanism
- nulliparity
- age >25 yr
- early menarche (<11-13 y/o), shorter menstrual cycles (defined as ≤27 d)

Sites of Occurrence

- ovaries: 60% of patients have ovarian involvement
- broad ligament, vesicouterine fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs and diaphragm

Clinical Features

- may be asymptomatic and can occur with one of 3 presentations

1. **pain** (80%)
   - menstrual symptoms
     - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
     - secondary dysmenorrhea
     - sacral backache with menses
     - pain may eventually become chronic, worsening perimenstrually
     - deep dyspareunia
   - bowel and bladder symptoms
     - frequency, dysuria, hematuria
     - cyclic diarrhea/constipation, hematochezia, dyschezia (suggestive of deeply infiltrating disease)
2. **infertility** (25%)
   - 30-40% of patients with endometriosis will be infertile
   - 15-30% of those who are infertile will have endometriosis
3. **mass (endometrioma)** (20%)
   - endometrioma: an endometriotic cyst encompassing ovary
   - ovarian mass can present with any of above symptoms or be asymptomatic
   - physical examination:
     - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
     - fixed retroversion of uterus
     - firm, fixed adnexal mass

Investigations

- definitive diagnosis can be made based on:
  - direct visualization of lesions typical of endometriosis at laparoscopy (gold standard)
  - biopsy and histologic exam of specimens 2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages
- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - "powder-burn" lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
- CA-125
  - may be elevated in patients with endometriosis but should NOT be used as a diagnostic test

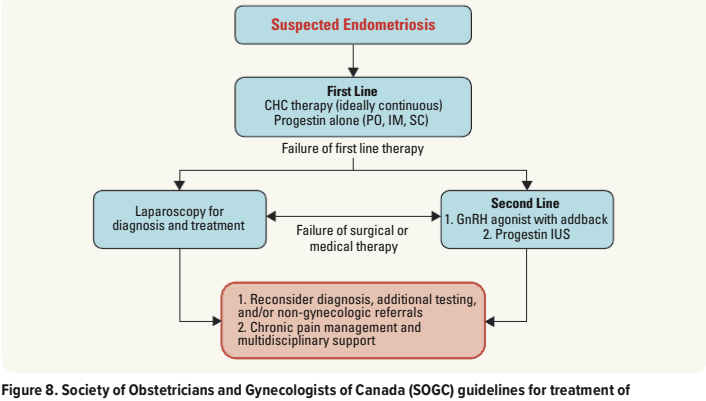

Suspected Endometriosis
First Line
CHC therapy (ideally continuous)
Progestin alone (PO, IM, SC)
Failure of first line therapy
Laparoscopy for diagnosis and treatment
Failure of surgical or medical therapy
Second Line
1. GnRH agonist with addback
2. Progestin IUS
1. Reconsider diagnosis, additional testing, and/or non-gynecologic referrals
2. Chronic pain management and multidisciplinary support

Figure 8. Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines for treatment of endometriosis

Long-Term Outcomes of Elagolix in Women with Endometriosis: Results from Two Extension Studies
Obstet Gynecol 2018;132:147-160
Purpose: An evaluation of the safety and efficacy of elagolix (a GnRH agonist) over 12 mo in women with endometriosis-associated pain.
Methods: A report of 2, double-blind, Phase III, placebo-controlled RCTs to evaluate two doses of elagolix over 12 mo of continuous treatment in patients with moderate to severe endometriosis-associated pain.
Results: In the first trial, 52.1% of women receiving 150 mg elagolix once daily had a clinical response with regards to dysmenorrhea and 67.8% had a response with regards to non-menstrual pelvic pain. In the higher dose group (200 mg q12 h), the response rate was 78.1% and 69.1%, respectively. These response rates were comparable in the second trial. Women who received elagolix had higher rates of hot flushes, higher serum lipids, and decreases in bone mineral density.
Conclusion: Both high and low doses of elagolix were effective in improving dysmenorrhea and non-menstrual pelvic pain in women with endometriosis-associated pain.

Endometriosis – Take Home Points

Suggestive history even with a negative exam should be considered adequate for a presumptive diagnosis

Pelvic pain that is not primary dysmenorrhea should be considered endometriosis until proven otherwise

Medical management is the mainstay of endometriosis

Consider surgery for patients who have not responded to medical management, fertility optimization, and/or large adnexal masses/adhesive disease causing obstruction. Medical management is often continued postoperatively

Treatment
- surgical confirmation of disease is NOT required prior to starting medical management. Asymptomatic endometriosis does not require treatment. Management depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)
- medical
  - medical suppression to prevent progression of disease, unless trying to conceive, which has not been proven in the literature
  - NSAIDs (e.g. naproxen sodium – Anaprox®). Avoid selective COX-2 inhibitors (celecoxib, rofecoxib, valdecoxib) in those who are attempting conception as some studies indicate these drugs can prevent or delay ovulation
  - 1st line
    - cyclic/continuous estrogen-progestin (OCP)
    - progestin (IM medroxyprogesterone (Depo-Provera®) or oral dienogest (Visanne®))
    - Mirena® IUS
  - 2nd line
    - GnRH agonist (e.g. leuprolide (Lupron®) or elagolix (Orlissa®)): suppresses pituitary gland and induces pseudomenopauses. Not a contraceptive
      - side effects: hot flashes, vaginal dryness, reduced libido
      - Lupron use >6 mo: include add-back progestin or estrogen to prevent decreased BMD, reduce vasomotor side effects
      - Orlissa® low dose (150 mg once daily) dose not require add-back progestin or estrogen. High dose (200 mg PO BID) dose require add-back
    - danazol (Danocrine®): weak androgen
      - side effects: weight gain, fluid retention, acne, hirsutism, voice change (not commonly used due to side effects)
- surgical
  - limited to failure of medical treatment, or desire for definitive treatment
  - conservative laparoscopy using laser, electrocautery ± laparotomy
    - ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  - definitive: hysterectomy ± bilateral salpingo-oophorectomy
  - best time to become pregnant is immediately after conservative surgery
  - if patient is not planning to become pregnant postoperatively, suppress ovulation medically to prevent recurrence (not proven)
- above treatments are for the pain, not for the infertility associated with endometriosis, which usually involves surgery + assisted reproductive technologies. Also, management for endometriomas is surgical for symptomatic and expanding masses, but this can decrease ovarian reserve, so if it is asymptomatic and small (<5 cm), then no surgery is necessary

Adenomyosis

Definition
- synonym: "endometriosis interna" (uterine wall may be diffusely involved)

Adenomyosis
Extension of areas of endometrial glands and stroma into the myometrium

Epidemiology
- 15% of females >35 y/o; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 y/o (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features
- often asymptomatic
- heavy menstrual bleeding, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm
- Halban's sign: tender, softened uterus on premenstrual bimanual exam

Final diagnosis of adenomyosis is based on pathologic findings, but predictably identified on MRI

Investigations
- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

Treatment
- medical
  - iron supplements for anemia
  - analgesics, NSAIDs
  - Mirena® IUS
  - CHC, dinogest (Visanne®), medroxyprogesterone (Depo-Provera®) – limited evidence for efficacy
  - GnRH agonists (e.g. leuprolide (Lupron ®), elagolix (Orlissa®))
  - danazol 100-200 mg PO once daily (trial x 4 mo)
- surgical
  - definitive: hysterectomy – treatment of choice in patients who have completed childbearing

Fibroids

Leiomyomata/Fibroids
Benign smooth muscle tumour of the uterus (most common gynecological tumour)

Submucosal leiomyomata are most symptomatic (bleeding, infertility)

Large fibroids can cause distressing bulk symptoms

The effect of pregnancy on fibroid size is variable

Epidemiology
- diagnosed in approximately 40-50% of premenopausal patients >35 yr
- more common in Black patients, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential
- typically regress after menopause

Pathogenesis
- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - fibroids can painfully degenerate, become calcified, develop sarcomatous component, or obtain parasitic blood supply

Classification
- International Federation of Gynecology and Obstetrics (FIGO) classifies fibroids by location and type
  - submucosal: grow within myometrium, can grow into endometrial cavity (FIGO type 0 - pedunculated, type 1 - <50% intramural, type 2 - ≥50% intramural)
  - intramural: most common, grow within the muscular wall of the uterus (FIGO type 3 - contacts endometrium and is 100% intramural, type 4 - intramural)
  - subserosal: grow from the serosa (FIGO type 5 - ≥ 50% intramural, type 6 - <50% intramural, type 7 - pedunculated)
  - cervical: located in cervix (FIGO type 8 - other)

Clinical Features
- majority asymptomatic, often discovered as incidental finding on pelvic exam or U/S (occur in 70-80% of women by age 50)
- symptoms classified into categories:
  - heavy or prolonged menstrual bleeding
    - AUB and menstrual cramps most common symptoms (26-29%) in symptomatic patients
  - pressure/bulk symptoms
    - pelvic pressure/heaviness
    - increased abdominal girth
    - urinary frequency, difficulty voiding
    - constipation, bloating (rare)
    - acute urinary retention (extremely rare, but surgical emergency!)
    - venous compression
  - reproductive dysfunction
    - infertility, recurrent pregnancy loss
    - pregnancy complications (fibroid degeneration, obstructed labour, malpresentation, difficult cesarean delivery)

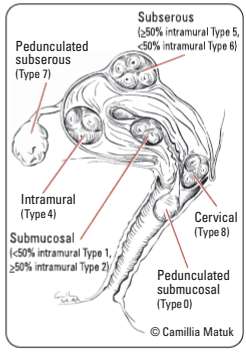


Figure 9. Possible anatomic locations of uterine leiomyomata

Investigations
- bimanual exam: uterus asymmetrically enlarged
- diagnosis typically made based on pelvic exam and pelvic U/S
- pelvic and/or transvaginal U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating polyps from submucosal fibroids, assessing size and degree of submucosal component, or assessing presence of submucosal fibroids which may impact fertility, or for planning hysteroscopic resection
- diagnostic office hysteroscopy: can be used instead of a sonohysterogram in patients with suspected submucosal fibroids or those desiring fertility to visualize the endometrial cavity, helps with planning of hysteroscopic submucosal fibroid resection, and rules out small polyps not visualized on U/S
- pregnancy test: performed for all patients of reproductive age via urine or serum pregnancy test to rule out pregnancy prior to start of the procedure
- occasionally MRI is used for preoperative planning (e.g. before consideration of laparoscopic myomectomy)
- endometrial biopsy: used in patients with AUB to rule out endometrial hyperplasia or cancer (especially if age >40 yr or risk factors (type 2 DM, obesity, chronic anovulation))
- CBC: anemia (only found if associated with AUB/heavy menstrual bleeding)

Treatment
- only if symptomatic (heavy menstrual bleeding, bulk symptoms), rapidly enlarging, or submucosal and affecting fertility
- whether patient desires fertility is key in guiding treatment options
- treat anemia if present
- conservative approach (watch and wait) if:
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant (follow-up U/S if symptoms progress-may remove at delivery if CD
- medical approach to treat AUB-L
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - CHC, hormonal IUS, or Depo-Provera®

Uterine Artery Embolization for Symptomatic Uterine Fibroids
Cochrane DB Syst Rev 2014;12:CD005073
Purpose: To compare outcomes of UAE to other. medical or surgical therapies for symptomatic uterine fibroids. Primary outcomes were patient satisfaction and live birth rate.
Results: Seven RCTs with 793 women were included. There was no evidence of a difference in the primary outcomes or risk of major complications between the interventions. UAE was associated with a higher risk of minor complications and the need for additional surgical intervention within 2 yr.
Conclusions: No significant differences in patient satisfaction or major complications in UAE compared to surgical intervention. UAE is associated with an increased risk of surgical re-intervention.

  - GnRH agonist: leuprolide (Lupron®)
    - often used for 3 mo preoperatively to increase Hb and reduce fibroid size
    - reduces bleeding, shrinks fibroids, and corrects anemia
    - can be used long-term to bridge to menopause in combination with add-back progestin or estrogen
- interventional radiology approach: UAE occludes both uterine arteries, shrinks fibroids by 50% at 6 mo; improves heavy bleeding in 90% of patients within 1-2 mo; not an option in patients considering childbearing
  - higher risk of surgical re-intervention than with surgical approaches
  - should not be considered in patients planning future pregnancies due to potential for pregnancy complications
  - patients can become septic while fibroid is degenerating and require emergency hysterectomy
  - best for bleeding symptoms and NOT bulk
- surgical approach
  - myomectomy (hysteroscopic, open, or laparoscopic)
  - hysteroscopic resection of fibroid and endometrial ablation for AUB-Lsm (ablation should not be performed in patients planning future pregnancies)
  - hysterectomy (see *Hysterectomy, GY6*)
  - note: traditionally avoid operating on fibroids during pregnancy (due to vascularity and potential pregnancy loss); expectant management is usually best but more recently becoming more common

Contraception

- see Family Medicine, FM23

Table 7. Classification of Contraceptive Methods

Type	Effectiveness (Perfect Use, Typical Use*)
Physiological	
Withdrawal/coitus interruptus	96%, 77%
Rhythm	76%
Method/calendar/mucus/symptothermal	98% (first 6 mo postpartum)
Lactational amenorrhea	15%
Abstinence of all sexual activity	100%
Barrier Methods	
Condom alone	98%, 82%
Spermicide alone	82%, 72%
Sponge	
Parous	80%, 76%
Nulliparous	91%, 88%
Diaphragm with spermicide	94%, 88%
Female condom	95%, 79%
Cervical cap	
Parous	74%, 68%
Nulliparous	91%, 84%
Hormonal **Combined (Estrogen and Progesterone)**	
OCP	99.7%, 92%
NuvaRing®	99.7%, 92%
Transdermal (Ortho Evra®)	99.7%, 92%
Progesterone-Only	
Progestin-only injection (Depo-Provera®)	99.7%, 97%
Mirena® IUS	99.9%
Etonogestrel implant (NEXPLANON®)	99%
Copper IUS	99.3%
Surgical	
Tubal ligation	99.65%
Vasectomy	99.9%
Emergency Postcoital Contraception (EPC)	
Yuzpe® method	98% (within 24 h), decreases by 30% at 72 h
Plan B® levonorgestrel only	98% (within 24 h), decreases by 70% at 72 h
Postcoital IUD	99.9% (within 7 d)
Ella®	99.9% (within 7 d)

*Effectiveness: percentage of patients reporting no pregnancy after 1 yr of use

Counselling the Adolescent about Contraception
More than 80% of adolescent pregnancies are unintended. The one-year risk of pregnancy for patients engaging in contraception is 85%. The Canadian Paediatric Society endorses long-acting reversible contraceptives (LARCs; subdermal contraceptives and intrauterine contraceptives) as first line options for Canadian youth

Hormonal Methods

Combined Oral Contraceptive Pills
- daily pill with a 4-7 d placebo or pill free break to allow for withdrawal bleed. This is an apparent period, originally devised for women to hide contraception from others, and is not the same as menstruation (shorter pill free intervals result in fewer unintended pregnancies)
- estrogen: suppresses FSH and follicular development
- progestin: prevents LH surge, suppresses ovulation, thickens cervical mucus, decreases tubal motility, decidualizes endometrium
- most contain low dose ethinyl estradiol (10-35 μg) plus progestin (norethindrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone). Pills vary by amount of ethinyl estradiol (maintains integrity of endometrium) and type of progestin (contraception action)
- failure rate (0.3-8.0%) depending on compliance
- monophasic formulations have the same amount of progestin throughout cycle while triphasic formulations have a varying amount of progestin throughout cycle
- can be prescribed for continuous or extended use. Continuous use involves taking a pill every day without using placebo pills, thus without withdrawal bleeding. Extended cycle preparations are also possible where withdrawal bleeds occur at less frequent intervals
- side effects: breast tenderness, nausea, bloating, unscheduled bleeding, amenorrhea. No clear evidence of weight gain
- risks: increased risk of venous thromboembolism, hypertension, and stroke in susceptible individuals. Unclear associations for elevated cancer risks
- non-contraceptive benefits: decreased menstrual bleeding, decreased acne, decreased progression of endometriosis as a result of inhibiting ovulation, decreased risk of ovarian and endometrial cancers

Transdermal (Ortho Evra®)
- patch that is changed every week for 3 consecutive weeks then left off for a week to allow for menstruation
- continuous release of norelgestromin 6 mg and ethinyl estradiol 0.60 mg into bloodstream
- can also be used in a continuous or extended fashion
- applied to lower abdomen, back, upper arm, buttocks, NOT breasts
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in patients >90 kg
- side effects: irregular uterine bleeding (worse at initiation), local skin irritation, breast tenderness, uncommonly mood disturbances
- should not be used in patients with skin hypersensitivity, exfoliative dermatologic disorders, or patients treated for Hepatitis C with obmitasvir, paritaprevir or ritonavir due to risk of reducing efficacy of the contraceptive

Contraceptive Ring (Nuva Ring®)
- thin flexible plastic ring that is inserted into the vagina by the patient and left there for 3 wk then removed and discarded. A new ring is then inserted 7 d later to allow for menstruation; releases etonogestrel 120 μg/d and estradiol 15 μg/d
- can also be used in a continuous or extended fashion
- as effective as OCP in preventing pregnancy (98%)
- side effects: vaginitis, vaginal discharge, mild breast tenderness, mild nausea
- associated with less breakthrough bleeding than other methods
- risk of toxic shock is rare

Starting Hormonal Contraceptives
- thorough history and BP measurement (post-pandemic SOGC guidelines do not require BP reading anymore to allow for virtual appointments)
- pelvic exam not required as STI screening can be done by urine, and pap smear screening does not start until >25 yr
- can start at any time during cycle but ideally within 5 d of LMP
- follow-up visit 3 mo after hormonal contraceptives prescribed
- generally recommended to use back-up contraception for 7 d, particularly if initiated >5 days from LMP

Table 8. Combined Estrogen and Progestin Contraceptive Methods

Advantages	Side Effects	Contraindications
Highly effective Reversible Cycle regulation Decreased dysmenorrhea and heavy menstrual bleeding (less anemia) Decreased benign breast disease and ovarian cyst development Decreased risk of ovarian and endometrial cancer Increased cervical mucus which may lower risk of STIs Decreased PMS symptoms Less acne Osteoporosis protection (possibly) Patient controlled	**Estrogen-related** Nausea Breast changes (tenderness, enlargement) Fluid retention/bloating/edema Weight gain (rare) Migraine, headaches Thromboembolic events Liver adenoma (rare) Breakthrough bleeding (low estradiol levels) **Progestin-related** Amenorrhea/breakthrough bleeding Headaches Breast tenderness Increased appetite Decreased libido Mood changes HTN Acne/oily skin* Hirsutism* *Androgenic side effects may be minimized by prescribing formulations containing desogestrel, norgestimate, drospirenone, or cyproterone acetate	**Absolute** 4 wk postpartum (breastfeeding) or <21 d postpartum (not breastfeeding) Major surgery with prolonged immobilization Known/suspected pregnancy Undiagnosed abnormal vaginal bleeding Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis Cerebrovascular or coronary artery disease Estrogen-dependent tumours (breast, uterus) Impaired liver function associated with acute liver disease Congenital hypertriglyceridemia Smoker age >35 yr Migraines with focal neurological symptoms (excluding aura) Uncontrolled HTN **Relative** Migraines (non-focal with aura <1 h) DM complicated by vascular disease SLE Controlled HTN Hyperlipidemia Sickle cell anemia Gallbladder disease **Drug Interactions/Risks** Rifampin, phenobarbital, phenytoin, griseofulvin, primidone, and St. John's wort can decrease efficacy of CHC requiring use of back-up method No evidence of fetal abnormalities if conceived on OCP No evidence that OCP is harmful to nursing infant but may decrease milk production

Table 9. Selected Examples of OCPs

Type	Active Compounds (estradiol and progestin derivative)	Advantages	Disadvantages
Lolo®	ethinyl estradiol 10 µg and norethindrone acetate 1 mg	Lowest estrogen dose (10 µg) OCP Least estrogen side effects 25% experience amenorrhea	Low-dose pills can often result in Low-dose pills can often result in breakthrough bleeding If this persists for longer than 3 mo, patient can be switched to an OCP with higher estrogen content Still effective with breakthrough bleeding
Alesse®	ethinyl estradiol 20 µg and levonorgestrel 0.5 mg	Low dose (20 µg) OCP Less estrogen side effects	Low-dose pills can often result in breakthrough bleeding If this persists for longer than 3 mo, patient can be switched to an OCP with higher estrogen content Still effective with breakthrough bleeding
Tri-cyclen®	ethinyl estradiol 35 µg and norgestimate 0.180/0.215/0.250 mg Triphasic oral contraceptive (graduated levels of progesterone)	Low androgenic activity can help with acne, as do all OCPs	Unlike monophasic OCP, triphasic OCPs cannot be used for continuous menstrual suppression as it will result in breakthrough bleeding
Yasmin® and Yaz®	Yasmin®: ethinyl estradiol 30 µg + drospirenone 3 mg (a new progestin) Yaz®: ethinyl estradiol 20 µg + drospirenone 3 mg – 24/4-d pill (4 d pill free interval) Drospirenone has antimineralocorticoid activity and antiandrogenic effects	Decreased perception of cyclic weight gain/bloating Fewer PMS symptoms Improved acne	Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency) Check potassium if patient also on ACEI, ARB, K+-sparing diuretic, heparin

Missed Combined OCPs

Miss 1 pill in <24 h
- Take 1 pill ASAP, and the next pill at the usual time

Miss ≥1 pill in a row in 1st wk
- Take 1 pill ASAP, and continue taking 1 pill daily until the end of the pack
- Use back-up contraception for 7 d; EPC may be necessary

Miss <3 pills in 2nd or 3rd wk of cycle
- Take 1 pill ASAP, and continue taking 1 pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- No need for back-up contraception

Miss ≥3 pills during the 2nd or 3rd wk
- Take 1 pill ASAP, and continue taking 1 pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- Use back-up contraception for 7 d; EPC may be necessary

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations. J Obstet Gynaecol Can 2008;30:1050-1062.

PROGESTIN-ONLY METHOD

Progestin-Only Pill

- progesterone-only pill taken daily with no pill free interval
- Slynd®: 4m g drospirenone - best for patients who need to avoid estrogen. Allows for 24 h missed-pill window. Formulated with 24 active pills and 4 placebo pills
- advantages: patient controlled, does not impact breast milk supply
- disadvantages: must take at exactly the same time every day so compliance can be challenging but has a 24 h missed pill window

Irregular breakthrough bleeding often occurs in the first few mo after starting OCP; usually resolves after three cycles

Progestin-only contraceptives must be taken at the same time every day

Progesterone Intrauterine System (IUS)

- small device left inside uterus typically left up to 5 yr, current FDA approved for up to 8 yrfor contraception
- Mirena IUS: levonorgestrel 52 µg - better for women patients with very heavy or painful periods, parous patients, 20% amenorrhea rate
- Kyleena IUS: levonorgestrel 19.5 µg - best for nulliparous people who want a light period every month and are mainly looking for birth control
- advantages: convenient, low hormone dose, minimal side effects, no effect on breast milk, quick return to fertility once removed
- disadvantages: insertion can be uncomfortable, must be inserted and removed by a doctor, rarely can have uterine perforation or IUS expulsion
- very effective reversible contraception; more likely to be an ectopic pregnancy if conception occurs due to efficacy at preventing intrauterine pregnancy. Lower absolute risk of ectopic pregnancy compared to other contraceptive methods

Depo-Provera®

- injectable depot medroxyprogesterone acetate 150 mg IM every 12 wk (convenient dosing)
- advantages: suppresses ovulation, complete amenorrhea in 70% of women after 1-2 yr of use, does not affect breast milk, effective for dysmenorrhea
- disadvantages: breakthrough bleeding, weight gain, controversial decreased bone density (often reversible), restoration of fertility may take up to 1-2 yr
- not recommended for long-term usage

Nexplanon®

- 4 cm long etonogestrel 68 mg implant that is placed in the inner arm and lasts for a maximum of 3 yr
- advantages: does not affect breast milk, do not have to put something in uterus, good bleeding and pain control, no change in bone density, quick return to fertility once removed
- disadvantages: breakthrough bleeding, weight gain

Table 10. Progestin-Only Contraceptive Methods

Indications	Mechanism of Action	Side Effects	Contraindications
Does not affect breast milk supply Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease) Women intolerant of estrogenic side effects of combined OCPs	Progestin prevents LH surge Thickening of cervical mucus Decreases tubal motility Endometrial decidualization Ovulation suppression – oral progestins do not consistently suppress ovulation compared to combined OCPs	Irregular menstrual bleeding Weight gain Headache Breast tenderness Mood changes Functional ovarian cysts Acne/oily skin Hirsutism	**Absolute** Current breast cancer Known/suspected pregnancy Undiagnosed vaginal bleeding Benign or malignant liver tumours, severe cirrhosis, or acute liver disease

Continuous or Extended Cycle vs. Cyclic Use of Combined Hormonal Contraceptives for Contraception
Cochrane Database Syst Rev 2014:7
Purpose: Systematic review of RCTs assessing the efficacy and side effects of cyclic administration vs. extended use (longer periods of active pills and/or shorter periods placebo) or continuous use (uninterrupted active pill administration) of combination oral contraceptives (COC).
Results: The initial review published in 2012 identified 12 RCTs that ultimately showed no difference between groups with regards to efficacy (pregnancy rates), safety, and compliance rates. Continuous or extended COCs were shown to reduce menstrual symptoms (headaches, tiredness, bloating, and menstrual pain). In addition, 11 of 12 studies reported similar or improved bleeding patterns with continuous or extended cycles.
Conclusions: This recently published updated systematic review identified a further 4 RCTs, however, results did not change.

Intrauterine Device

Table 11. IUS Contraceptive Methods

Mechanism of Action	Benefits of all IUS	Risks of all IUS	Side Effects	Contraindications
Copper-Containing IUS (Nova-T®): mild foreign body reaction in endometrium, toxic to sperm and alters sperm motility **Progesterone-Releasing IUS (Mirena®, Kyleena®):** decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation	Return to baseline fertility after removal is very fast No estrogen (doesn't affect breastfeeding, can use if smoker, hypertension, previous VTE) Lasts 5 yr but can be removed before that if desired Can insert immediately after placental delivery and post abortion	Insertion is uncomfortable Must be inserted and removed by a doctor Infection (especially if multiple partners and within first 10 d of insertion) Uterine wall perforation on insertion (1/10000) Expulsion (5% in the 1st yr, greatest in the 1st mo) Chance of pregnancy very low, but if pregnant, higher relative risk of an ectopic pregnancy or miscarriage IUS do not protect against STIs*	**Copper IUS:** increased blood loss and duration of menses, dysmenorrhea, increased vaginal discharge **Progesterone IUS:** spotting, bloating, headache, acne, breast tenderness, nausea, headaches, ovarian cyst formation, vaginal discharge, and/or mood changes. Usually very mild	**Absolute** **Both Copper and Progesterone IUS** Known or suspected pregnancy Undiagnosed genital tract bleeding Acute or chronic PID Lifestyle risk for STIs Known distorted uterine cavity Immediately post-septic abortion **Copper IUS** Known allergy to copper or Wilson's disease **Relative** **Both Copper and Progesterone IUS** Valvular heart disease PMHx of PID or ectopic pregnancy Presence of prosthesis Abnormalities of uterine cavity Intracavitary fibroids Cervical stenosis Immunosuppressed individuals (e.g. HIV) Abnormalities of uterine cavity (excluding distorted uterine cavity) Copper IUS – severe dysmenorrhea or heavy menstrual bleeding

*Cervical swabs for gonorrhea and chlamydia should be done prior to insertion

Emergency Postcoital Contraception

Table 12. Emergency Postcoital Contraceptive (EPC) Methods

Method	Mechanism of Action	Side Effects	Contraindications
HORMONAL			
Yuzpe Method Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg levonorgestrel 500 µg) Can substitute with any OCP as long as it contains ethinyl estradiol 100 µg 2% overall risk of pregnancy Used within 72 h of unprotected intercourse ideally within 24 h intercourse, limited evidence of benefit up to 5 d Efficacy decreased with time (e.g. less effective at 72 h than 24 h)	Unknown; theories include: Suppresses ovulation or causes deficient luteal phase Alters endometrium to prevent implantation Affects sperm/ova transport	Nausea (due to estrogen; treat with Gravol®) Irregular spotting	Pre-existing pregnancy (although not teratogenic) Caution in women with contraindications to OCP (although no absolute contraindications)
"Plan B™" Use within 72 h of unprotected intercourse, can use up to 5 d after levonorgestrel 750 µg q12 h for 2 doses (can also take 2 doses together) Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method No estrogen thus very few contraindications/side effects (less nausea) Less effective if >75 kg, not recommended if >80 kg	Same as above	Same as above	Same as above but no caution in women with contraindications to OCP
Ulipristal (Ella™) 30 mg PO within 5 d of unprotected intercourse	Selective Progesterone Receptor Modulator (SPRM) with primarily antiprogestin activity: may delay ovulation by up to 5 d	Headache, hot flashes, constipation, vertigo, endometrial thickening	Same as above but no caution in women with contraindications to OCP Need to delay the restart of Combined OCP by 14 d
NON-HORMONAL			
Postcoital IUD (Copper) Insert up to 7 d postcoitus Prevents implantation 1% failure rate Can use for short duration in higher risk individuals	See *Table 11*, GY18	See *Table 11*, GY18	See *Table 11*, GY18

Follow-up
- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counselling

Termination of Pregnancy

Indications
- patient desires an end to pregnancy
- may be for medical reasons (health of patient, disorders of pregnancy, or fetal anomaly) or a variety of social reasons, including patient

Legal Considerations
- no current law in Canada concerning abortion. Access to abortion is provincially regulated and highly variable
- CPSO: a physician must provide a referral for abortion services regardless of personal beliefs, but is not compelled to personally perform the procedure

Rates
- 13.1 abortions in 1000 women 15-44 yr in Canada (2017 CIHI data)
- worldwide: 56 million induced abortions per yr; half are unsafe (WHO data)
- maternal mortality almost zero where induced abortion is safe and legal; rises to 100 maternal deaths in 100000 live births in sub-Saharan Africa and other countries where abortion is illegal and unsafe
- in Canada, 91% of induced abortions occur <12 wk GA; much less common after 24 wk GA (usually only for maternal/fetal reasons)

Methods of Induced Abortion
- medical
  - gold standard up to 9 wk GA
  - mifepristone and misoprostol 95-98% effective up to 49 d after LMP
  - mifepristone (200 mg PO on 1st d) blocks the progesterone receptor (progesterone required in early pregnancy), alters the endometrium, induces bleeding and causes the cervix to soften
  - misoprostol (800 mg PV/BUC on 2nd or 3rd d) is a synthetic prostaglandin that stimulates uterine contractions and expulsion of the products of conception
  - can also use misoprostol alone or methotrexate and misoprostol (with lower success rates of 90-95%)

- good follow-up and back-up access to D&C required if medical abortion fails
- side effects: bleeding (self-limited) and pain (while tissue passes) are expected side effects, as well as nausea, diarrhea, and chills/fever due to prostaglandin effects
- contraindications:
  - absolute: ectopic pregnancy, chronic adrenal failure, ambivalence
  - relative: unconfirmed GA, IUD in situ, long term steroid therapy, bleeding disorder/anticoagulation, porphyria
- between 14-24 wk GA medical induction of labour (misoprostol followed by oxytocin) is an option, whereas after 24 wk GA induction of labour is the only option

- surgical
  - <14 wk GA:
    - manual vacuum aspiration – up to 12 wk GA with handheld aspiration device
    - suction dilatation + aspiration ± curettage – may involve presurgical preparation of cervix with laminaria tents and/or misoprostol
  - 14-24 wk GA:
    - dilatation and evacuation - presurgical preparation of cervix required with laminaria tents
  - pain or discomfort during procedure mitigated by use of appropriate analgesia/sedation/anesthesia (including paracervical blocks)
  - rare complications (1-5%): laceration of cervix, infection/endometritis, retained products of conception, ongoing pregnancy
  - very rare complications (0.1-2%): hemorrhage, perforation of uterus, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), future preterm birth (controversial and likely only with repeated abortion)
- counselling
  - counselling options always provided including possibility of carrying pregnancy with/without adoption
  - offer future contraception (most effective way to prevent unintended pregnancies) and family planning services
  - ensure follow-up

Pregnancy-Related Complications

First Trimester Bleeding

Prevalence
- first trimester (T1) vaginal bleeding or spotting is common, occurring in 25% of pregnancies

Approach to the Patient with Bleeding in First Trimester

History
- risk factors for ectopic pregnancy (see *Ectopic Pregnancy, GY21*)
- previous spontaneous abortion
- recent trauma
- characteristics of the bleeding (including any tissue passed)
- characteristics of the pain (cramping pain suggests spontaneous abortion)
- history of coagulopathy
- gynecological/obstetric history
- fatigue, dizziness, syncopal episodes due to hypovolemia, fever (may be associated with septic abortion)

Physical
- vitals (including orthostatic changes)
- abdomen (symphysis fundal height, tenderness, presence of contractions)
- perineum (signs of trauma, genital lesions)
- speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness, cervical motion tenderness)

Investigations
- β-hCG
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Bleeding in Pregnancy Definitions

First trimester bleeding: vaginal bleeding within the first 14 wk

Second trimester bleeding: 14-28 wk

Differential Diagnosis

Physiologic bleeding: spotting, due to implantation of placenta – reassure and check serial β-hCGs

Abortion (threatened, inevitable, incomplete, complete)

Abnormal pregnancy (ectopic, molar) (see *Hydatidiform Mole, GY53*)

Trauma (post-coital or after pelvic exam)

Genital lesion (e.g. cervical polyp, neoplasms)

Subchorionic hematoma

Non-OB/GYN related cause of bleeding (e.g. hemorrhoids)

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured

Spontaneous Abortions

- see *Termination of Pregnancy, GY19* for therapeutic abortions

Table 13. Classification of Spontaneous Abortions

Type	History	Clinical and U/S Findings	Management (± Rhogam®)
Threatened	Bleeding ± cramping	Live fetus on U/S Cervix closed	Watch and wait <5% will go on to abort
Inevitable	Bleeding and cramping ± rupture of membranes	Fetus low in uterus on U/S Cervix open	a) Watch and wait b) Misoprostol 800 µg PV now and 800 µg PV 24 h later c) D&C
Incomplete	Bleeding and cramps ± passage of tissue noticed	Residual tissue in uterus on U/S Cervix open	a) Watch and wait b) Misoprostol 800 µg PV now and 800 µg PV 24 h later c) D&C
Complete	Bleeding and complete passage of sac and placental tissue	Empty uterus on U/S Cervix closed, no bleeding	No management needed
Missed	No bleeding (fetal death in utero)	No fetal heart rate on U/S, fetus and sac still in uterus Cervix closed, no bleeding	a) Watch and wait b) Mifepristone 200 mg PO followed by misoprostol 800 µg PV 24 h later c) D&C
Recurrent	≥3 consecutive spontaneous abortions		Evaluate mechanical, genetic, environmental, and other risk factors
Septic	Contents of uterus infected – very rare	Tissue in uterus on U/S Foul discharge	a) IV broad spectrum antibiotics b) D&C 24 h after antibiotics c) Misoprostol 800µg PV 24 h later

Management of Abortions

Always rule out an ectopic pregnancy

Always check Rh; if negative, give Rhogam®

Always ensure patient is hemodynamically stable

Pregnancy failure can be diagnosed on U/S based on findings of crown-rump length ≥7 mm and no heartbeat, mean sac diameter of ≥7 mm and no embryo, absence of embryo with heartbeat ≥2 wk after a scan that showed a gestational sac without a yolk sac, or absence of embryo with heartbeat ≥11 d after a scan that showed a gestational sac with a yolk sac

Ectopic Pregnancy

Definition

- embryo implants outside of the endometrial cavity

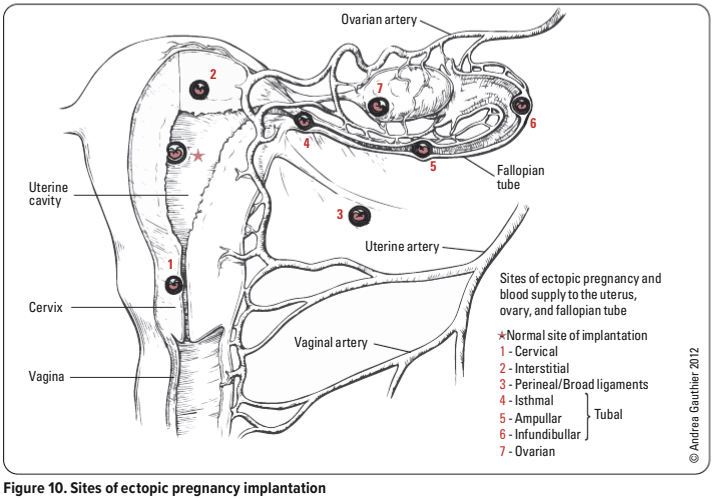


Figure 10. Sites of ectopic pregnancy implantation
ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

Epidemiology

- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of maternal death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

Etiology

- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle

- transmigration of fertilized ovum to contralateral tube
- major cause is disruption of normal tubal anatomy (infection, surgery, congenital differences, tumours)

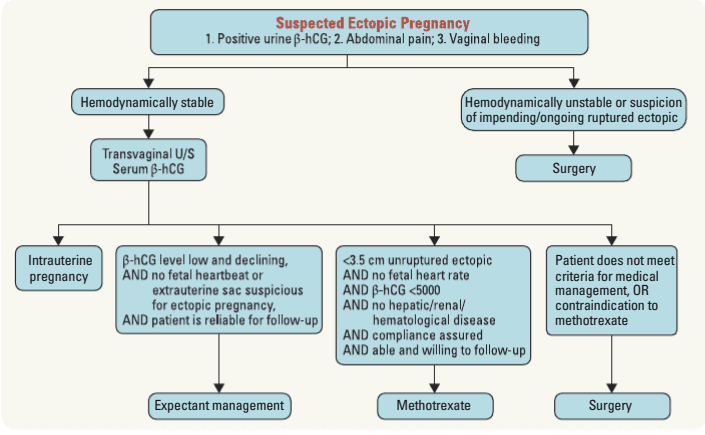

Suspected Ectopic Pregnancy
1. Positive urine β-hCG; 2. Abdominal pain; 3. Vaginal bleeding
Hemodynamically stable
Hemodynamically unstable or suspicion of impending/ongoing ruptured ectopic
Transvaginal U/S Serum β-hCG
Surgery
Intrauterine pregnancy
β-hCG level low and declining, AND no fetal heartbeat or extrauterine sac suspicious for ectopic pregnancy, AND patient is reliable for follow-up
<3.5 cm unruptured ectopic AND no fetal heart rate AND β-hCG <5000 AND no hepatic/renal/ hematological disease AND compliance assured AND able and willing to follow-up
Patient does not meet criteria for medical management, OR contraindication to methotrexate
Expectant management
Methotrexate
Surgery

Figure 11. Algorithm for suspected ectopic pregnancy

Risk Factors

- previous ectopic pregnancy
- gynecologic
  - current IUD use – overall risk of pregnancy very low, but increased risk of ectopic pregnancy if pregnancy occurs
  - history of PID (especially infection with *C. trachomatis*), salpingitis, gonorrhea, chlamydia
  - infertility
- infertility treatment (IVF pregnancies following ovulation induction (7% ectopic rate))
- previous procedures
  - any surgery on fallopian tubes (for previous ectopic pregnancy, tubal ligation, tubal reconstruction, etc.)
  - abdominal surgery for ruptured appendix, etc.
- smoking
- structural
  - uterine leiomyomas
  - adhesions
- *in utero* diethylstilbestrol (DES) exposure
- regular vaginal douching
- increased age

Investigations

- serial β-hCG levels; normal doubling time with intrauterine pregnancy is every 48 h in the first 8 wk
  - rise in β-hCG <35% every two days across 3 measurements is consistent with a non-viable pregnancy
  - prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - extra-uterine gestational sac with a yolk sac or embryo, regardless of cardiac activity, is diagnostic
  - specific suggestive, but not diagnostic, finding on transvaginal U/S is a tubal ring
- suspect ectopic pregnancy in case of empty uterus by transvaginal U/S with β-hCG >2000-3000 mIU/mL
- laparoscopy (sometimes used for definitive diagnosis)

Treatment

- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical = laparoscopy
  - linear salpingostomy an option if tube salvageable, however, patient must be reliable to follow-up with weekly β-hCG
  - 15% risk of persistent trophoblast if salpingostomy, must monitor β-hCG titres weekly until they reach non-detectable levels
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence

Contraindications to Methotrexate Therapy in the 2021 SOGC Clinical Practice Guidelines on Management of Pregnancy of Unknown Location, Tubal and Nontubal Ectopic Pregnancies.
J Obs Gyn Can 2021; 43(5): 614-630

1. Hemodynamic instability or any signs of hemorrhage or tubal rupture
2. Unwilling or unable to adhere to methotrexate protocol and follow-up
3. Clinically significant abnormalities in renal or liver function
4. Hematologic disorders or bone marrow suppression
5. Active pulmonary disease
6. Peptic ulcer disease
7. Hypersensitivity to methotrexate
8. Immunosuppression or immunodeficiency
9. Chronic infection
10. Heterotopic pregnancy with coexisting viable intrauterine pregnancy
11. Breastfeeding

Note - cannot conceive for 3 mo after methotrexate therapy due to high teratogenicity

Salpingostomy Versus Salpingectomy in Women with Tubal Pregnancy (ESEP study): An Open-Label, Multicentre, Randomized Controlled Trial
Lancet 2014; 383:1483-1487

Purpose: Determine whether tube preserving salpingostomy offers favorable future fertility compared to salpingectomy in patients surgically treated for tubal pregnancies.
Methods: In this international RCT, patients with confirmed tubal pregnancy and healthy contralateral tube were randomized to salpingostomy (n=215) and salpingectomy (n=231). The primary outcome was ongoing pregnancy by natural conception.
Results: The primary outcome was present in 60.7% of patients in the salpingostomy group and 56.2% of patients in the salpingectomy group (p = 0.678). Persistent trophoblast was more frequent in the salpingostomy group with 7% of patients compared to <1% of patients in the salpingectomy group.
Conclusions: For pregnant patients requiring surgical treatment for tubal pregnancy, and that have a healthy contralateral tube, salpingostomy does not increase fertility prospects.

DDx of Lower Abdominal Pain
Urinary tract: UTI, kidney stones
GI: diverticulitis, appendicitis
Gynecological: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

Any patient with a uterus presenting with abdominal pain, vaginal bleeding, and amenorrhea is an ectopic pregnancy until proven otherwise

More than half of patients with ectopic pregnancy have no risk factors

- consider Rhogam® if Rh-negative
- patient may require laparotomy if unstable, extensive abdominal surgical history, etc.

- medical = methotrexate
  - folic acid reductase inhibitor affecting rapidly dividing cells
  - use 50 mg/m²body surface area; given as a one time IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)
  - follow β-hCG levels on days 4 and 7 after injection, and then weekly until β-hCG is non-detectable
  - plateaued or rising levels suggest persistent trophoblastic tissue requiring further treatment
  - 82-95% success rate, but up to 25% will require a second dose
  - administer a second dose if β-hCG does not decrease by at least 15%
  - tubal patency following methotrexate treatment approaches 80%
  - stop prenatal vitamins as folic acid will decrease efficacy of methotrexate
- expectant management is an option for patients who are clinically stable, reliable for follow-up, understand the risk of tubal rupture, and have β-hCG levels that are low and declining

Presentation of Ectopic Pregnancy Ruptures

Acute abdomen with increasing pain

Abdominal distention

Shock

Prognosis

- 9% of maternal deaths during pregnancy attributed to ectopic pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

Infertility

Epidemiology

- 10-15% of couples, must investigate both members of the couple

Female Factors

Infertility: inability to conceive or carry to term a pregnancy after 1 yr of regular, unprotected intercourse
Primary infertility: infertility in the context of no prior pregnancies
Secondary infertility: infertility in the context of a prior conception
Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr

Etiology

- increasing age
- chemotherapy
- ovulatory dysfunction (15-20%)
  - three groups of ovulatory disorders
    - hypogonadotropic hypogonadal (hypo-hypo; low gonadotropins, low gonadal hormones) anovulation (5-10%): excessive exercise, low body weight
    - normogonadotropic normoestrogenic anovulation (70-85%): PCOS
    - hypergonadotropic hypoestrogenic anovulation (10-30%): primary gonadal failure, gonadal dysgenesis
  - hypothalamic (hypothalamic amenorrhea)
    - stress, poor nutrition, excessive exercise (even with presence of menstruation), history of eating disorders
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - PCOS
    - primary ovarian insufficiency
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, diabetes, Cushing's syndrome, renal/hepatic failure)
  - congenital (Turner's syndrome, gonadal dysgenesis, gonadotropin deficiency)
- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - PID
    - adhesions (previous surgery, peritonitis, endometriosis)
    - ligation/occlusion (previous ectopic pregnancy)
- uterine factors (<5%)
  - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure, intrauterine adhesions (e.g. Asherman's syndrome), submucosal fibroids/polyps
  - infection (endometritis, pelvic tuberculosis)
- cervical factors (5%)
  - hostile or acidic cervical mucus, anti-sperm antibodies
  - structural defects (cone biopsies, laser or cryotherapy)
- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

When Should Investigations Begin?

- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo of regular unprotected intercourse
- >40 yr: immediately

Earlier if:

- History of PID
- History of infertility in previous relationship
- Prior pelvic surgery
- Chemotherapy/radiation in either partner
- Recurrent pregnancy loss
- Moderate-severe endometriosis

Investigations

- ovarian factors
  - day 3: FSH, LH, estradiol, TSH, prolactin, free and total testosterone, androstenedione, DHEAS, free testosterone
  - day 21-23: high serum progesterone levels confirm ovulation

Ethical Considerations in Infertility Treatment

Infertility demands non-judgmental discussion

Ethical issues surrounding surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial

If the physician finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

- general health: CBC, Fe, HbA1c
- any day of cycle: anti-mullerian hormone (AMH) – a test of ovarian reserve, the higher the number the better

• tubal factors
- hysterosalpingogram (HSG) – dye insufflated into uterus and x-ray taken
  - shows uterine cavity shape and if tubes are patent
  - can be therapeutic – opens fallopian tube
- sonohysterogram (SHG) – saline insufflated into uterus and U/S done
  - shows uterine cavity shape and if tubes are patent
  - can be therapeutic and opens the tubes
- laparoscopy with dye insufflation (or tubal dye test) rarely done as diagnostic

• peritoneal/uterine factors
- HSG/SHG, hysteroscopy

• other
- karyotype

Treatment

• lifestyle modifications (quit smoking/cannabis, reduce caffeine/alcohol intake, healthy diet, exercise, etc.)
- education: time intercourse relative to ovulation (have sex every other day from 4 d prior to 2 d following presumed ovulation)

• medical
- ovulation induction
  - clomiphene citrate (Clomid®): estrogen antagonist used in anovulatory patients
    - blocks brain's perception of circulating estrogen, resulting in increased release of FSH and LH which can help to induce ovulation (better results if anovulatory)
  - letrozole: aromatase inhibitor; may be associated with a higher rate of live births in patients with PCOS
- may add:
  - bromocriptine (dopamine agonist) or carbamazepine (anticonvulsant) if elevated prolactin
  - metformin (for PCOS)
  - luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
  - anticoagulation and ASA (81 mg PO once daily) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
  - thyroid replacement to keep TSH <2.5

• procedural
- artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
- sperm washing
- IVF
- intrafallopian transfer (IFT)
- GIFT*: immediate transfer with sperm after oocyte retrieval
- ZIFT*: transfer after 24 h culture of oocyte and sperm
- TET*: transfer after >24 h culture
- ICSI
- IVM
- ± oocyte or sperm donors
- ± pre-genetic screening for single gene defects in karyotype of zygote
- hysteroscopy

*not performed in Canada

• surgical
- salpingectomy
- tubuloplasty (extremely rare)
- lysis of adhesions

Male Factors

- see Urology, U24

Etiology

- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)
- exogenous androgens

Investigations

- semen analysis and culture

Normal Semen Analysis (WHO lower reference limits)
- Must be obtained after 2-7 d of abstinence
- Volume 1.5 cc
- Count 15 million/cc
- Vitality 58% live
- Motility 32% progressive, 40% total (progressive + non-progressive)
- Morphology 4.0% normal

Polycystic Ovarian Syndrome

Etiology

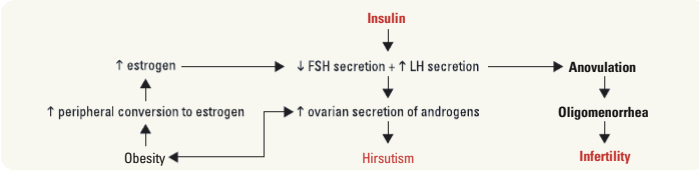


Figure 12. Pathophysiology of polycystic ovarian syndrome

Diagnosis

- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence – hirsutism or acne
    - biochemical evidence – raised free testosterone
  - polycystic ovaries on U/S (not appropriate in adolescents)

Clinical Features

- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis as adolescence resembles PCOS
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- acanthosis nigricans: darkening of skin folds in intertriginous zones (indicative of insulin resistance)
- insulin resistance occurs in both lean and obese patients
- FHx of DM

Investigations

- assess BMI, BP, and fasting lipid profile at presentation
  - goal: identify hyperandrogenism or chronic anovulation and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, TSH, free T4
  - 17-hydroxyprogesterone, LH:FSH >2:1 (LH is chronically high with FSH mid-range or low (low sensitivity and specificity))
  - increased DHEAS, androstenedione, and free testosterone (most sensitive)
- transvaginal or transabdominal U/S: polycystic-appearing ovaries
  - "string of pearls" – 12 small follicles 2-9 mm or increased ovarian volume (>10 cc)
- tests for insulin resistance or glucose tolerance
  - 75 g OGTT every other year (particularly if obese)
- consider endometrial biopsy if long-standing abnormal uterine bleeding to rule out hyperplasia
- rule out other causes of abnormal bleeding

Treatment

- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - hormonal IUS, combined hormonal contraception or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if T2DM or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only
- infertility
  - medical induction of ovulation: letrozole, clomiphene citrate, human menopausal gonadotropins (HMG (Pergonal®)), LHRH, recombinant FSH, and metformin
    - metformin may be used in conjunction with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary - rarely done
  - bromocriptine (if hyperprolactinemia)
- hirsutism
  - any OCP can be used
    - Diane 35® (cyproterone acetate): antiandrogenic
    - Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
  - finasteride (5-α reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone (androgen receptor inhibitor)

Polycystic Ovarian Syndrome
HHAIIR-AN
Hirsutism, **H**yper**A**ndrogenism, **I**nfertility, **I**nsulin **R**esistance, **A**canthosis **N**igricans

PCOS may be confused with
- Late onset CAH (21-hydroxylase deficiency)
- Cushing's syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism

Clinical Signs of Endocrine Imbalance
- Menstrual disorder/amenorrhea (80%)
- Infertility (74%)
- Hirsutism (69%)
- Obesity (49%)
- Impaired glucose tolerance (35%)
- DM (10%)

Long-Term Health Consequences
- Hyperlipidemia
- Adult-onset DM
- Endometrial hyperplasia
- Subfertility
- Obesity
- Sleep apnea

Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies
J Obstet Gynaecol Can 2008;8:671-679
At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also the inappropriate tendency to assign ovulatory status solely on the basis of menstrual cycle history or poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multifactorial and complex nature of PCOS and place this in the context of our present diagnostic limitations.

Gynecological Infections

Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 4.0-4.5
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Non-Physiologic Discharge

- etiology
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen vascular disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)

Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features: irritation, pruritus, discharge, vulvar erythema, vaginal bleeding (can be due to Group A *Streptococcus* and *Shigella*)
- etiology
  - non-specific vulvovaginitis is responsible for 25-75% of vulvovaginitis in prepubertal patients
  - there are a number of potential factors in children that increase the risk of vulvovaginitis:
    - lack of labial development
    - non-estrogenized, thin mucosa
    - more alkaline pH (pH >7) than postmenarchal patients
    - obesity
    - poor hygiene (proximity of anus to vagina)
    - foreign bodies (most commonly toilet paper)
    - irritation by bubble baths, shampoos, perfumed soaps, and chemicals
  - localized skin disorders: lichen sclerosis, condyloma acuminata
  - trauma: accidental straddle injury, sexual abuse
  - infectious
    - pinworms
    - *Candida* (if using diapers or chronic antibiotics)
    - Group A *Streptococcus, S. aureus*, and *Shigella*
    - discovery of STI should raise suspicion of sexual abuse
  - other
    - polyps, tumour (ovarian malignancy)-RARE
    - psychosomatic vaginal complaints (specific to vaginal discharge)
    - endocrine abnormalities (specific to vaginal bleeding)
    - blood dyscrasia (specific to vaginal bleeding)
    - other systemic diseases: measles, chickenpox, scarlet fever, Epstein-Barr Virus, *Mycoplasma* pneumonia-induced rash and mucositis, Stevens-Johnson syndrome, Crohn's disease, and Kawasaki disease have all been associated with vulvovaginal signs and symptoms
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
  - pH, wet-mount, and KOH smear in postpubertal adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, use sitz baths, use mild detergent, urinate with legs spread apart, no nylon tights, no tight-fitting clothes, no sleeper pajamas, avoid bubble baths, eliminate fabric softener, avoid prolonged exposure to wet bathing suits) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

Vulvovaginitis
Vulvar and vaginal inflammation

Vulvar Hygiene
Recommend wipe front to back, wash vulva only with water, avoid daily pantyliners, avoid douching, no need for "feminine cleansers/sprays/powders," use gentle laundry detergents for underwear, cotton underwear, no underwear at night

Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality

Clinicians who treat adolescents must be aware of federal, state, and provincial laws related to adolescent consent and confidentiality

Clinicians must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice

Most common gynecological problem in prepubertal patients is non-specific vulvovaginitis, not yeast

Table 14. Other Common Causes of Vulvovaginitis in Prepubertal Girls

	Pinworms	Lichen Sclerosis	Foreign Body
Diagnosis	Cellophane tape test	Area of white patches and thinning of skin (figure of 8)	Careful examination with or without sedation
Treatment	Empirical treatment with mebendazole (anthelmintic)	Topical steroid creams	Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia

INFECTIOUS VULVOVAGINITIS

Table 15. Infectious Vulvovaginitis

	Candidiasis	Bacterial Vaginosis (BV)	Trichomoniasis
Organisms	*Candida albicans* (90%) *Candida glabrata* (<5%) *Candida tropicalis* (<5%)	Replacement of vaginal Lactobacillus with: *Gardnerella vaginalis* *Mycoplasma hominis* *Anaerobes: Prevotella, Mobiluncus, Bacteroides*	*Trichomonas vaginalis* (flagellated protozoan)
Risk Factors	Immunosuppression (DM, AIDS, etc.) Recent antibiotic use Increased estrogen levels (e.g. pregnancy, OCP)	High frequency of vaginal intercourse Smoking Douching	Sexual transmission
Discharge	Whitish, "cottage cheese," minimal	Grey, thin, diffuse, fishy smelling	Yellow-green, malodourous, diffuse, frothy
% asymptomatic	20% asymptomatic	50-75% asymptomatic	25% asymptomatic
Signs/Symptoms	Intense pruritus Swollen, inflamed genitals Vulvar burning, dysuria, dyspareunia	Fishy odour, especially after coitus Absence of vulvar/vaginal irritation	Petechiae on vagina and cervix Occasionally irritated, tender vulva Dysuria, frequency, dyspareunia
pH	≤4.5	≤4.5	≤4.5
Saline Wet Mount	KOH wet mount reveals hyphae and spores	>20% clue cells = squamous epithelial cells dotted with coccobacilli (*Gardnerella*) Paucity of WBC Paucity of Lactobacilli Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)	Motile flagellated organisms Many WBC Inflammatory cells (PMNs) Can have positive whiff test
Treatment	Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments Only vaginal treatment in pregnancy Fluconazole 150 mg PO in single dose	No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure **Oral** Metronidazole 500 mg PO BID x 7 d* Oral treatment is best in pregnancy **Vaginal** Metronidazole 0.75% gel x 5 d once daily Clindamycin 2% 5 g intravaginally at bedtime for 7 d Probiotics (*Lactobacillus* sp.): oral or topical alone or as adjuvant	Treat even if asymptomatic Metronidazole 2 g PO single dose or metronidazole 500 mg BID x 7 d (alternative) Symptomatic pregnant women should be treated with metronidazole 2 g once
Other	Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole Routine treatment of partner(s) not recommended (not sexually transmitted)	Associated with recurrent preterm labour, preterm birth, and postpartum endometritis Routine treatment of partner(s) not recommended (not sexually transmitted)	Treat partner(s) (sexually transmitted)

* Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)

Sexually Transmitted Infections

- see Family Medicine, FM46

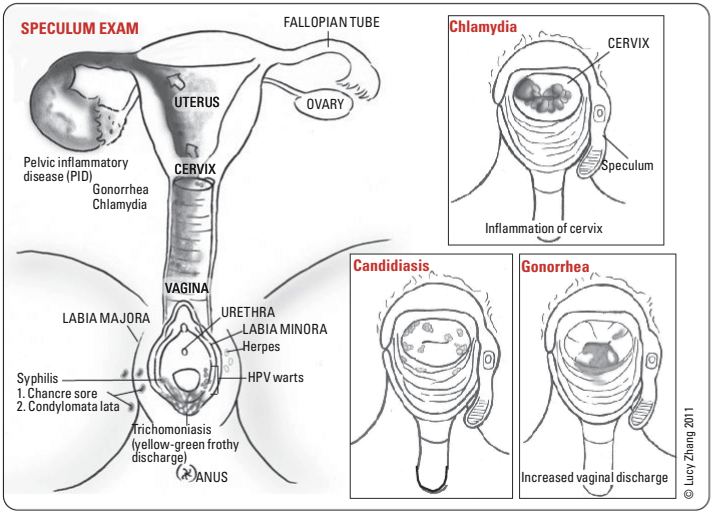


Figure 13. Speculum exam

CDC Notifiable Diseases
- Chancroid
- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis

Risk Factors for STIs
- History of previous STI
- Contact with infected person
- Sexually active individual <25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Social factors (homelessness, drug use)

TRICHOMONIASIS

- see *Infectious Vulvovaginitis, GY27*

CHLAMYDIA

Etiology

- *Chlamydia trachomatis*

Epidemiology

- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae* (patients with chlamydia should also be tested for gonorrhea)

Clinical Features

- asymptomatic (80% of patients)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

Investigations

- cervical culture or nucleic acid amplification test (can present in pharynx, rectum)
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and self-administered vaginal tests now available, which are equally or more effective than cervical culture

STI Testing
- Vaginal swab
- Tests for bacterial vaginosis, trichomoniasis, *Candida*
- Cervical swab
- Tests for gonorrhea and chlamydia

Treatment

- doxycycline 100 mg PO BID for 7 d or azithromycin 1 g PO in a single dose
  - doxycycline is contraindicated in the 2nd and 3rd trimesters of pregnancy
- reportable disease to public health
- test and provide empiric treatment to all sexual partners of the index case within 60 d prior to symptom onset or date of specimen collection (if the index case is asymptomatic)
- test of cure is recommended 3 wk after completion of treatment when compliance to treatment is suboptimal, an alternative treatment regimen is used, persistent symptoms, or the person is prepubertal or pregnant

Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated
Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant

Screening

- during pregnancy
- asymptomatic sexually active people under 25 yr
- neonates born to mothers with chlamydia
- any other people with risk factors for sexually transmitted and blood-borne infections

Complications
- PID: low-grade salpingitis and adhesions resulting in tubal obstruction
- infertility
- ectopic pregnancy
- chronic pelvic pain
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- perinatal infection: conjunctivitis, pneumonia

GONORRHEA

Etiology
- *Neisseria gonorrhoeae*
- symptoms and risk factors same as chlamydia

Investigations
- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal, and throat culture (if clinically indicated)

Treatment
- single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
  - if pregnant: above regimen or spectinomycin 2 g IM plus azithromycin 1 g PO (avoid quinolones)
  - also treat chlamydia, due to high rate of co-infection
- treat partners
  - reportable disease
  - screening as with chlamydia

HUMAN PAPILLOMAVIRUS

Etiology
- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma
  - HPV is readily transmissible between opposite and same-sex partners through receptive and penetrative vaginal, anal and oral sex, and non-penetrative sex (digital-vaginal sex and skin-to-skin contact)
  - infection with one HPV type does not appear to provide protection against infection with related HPV types

Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification (check pharynx too)
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

Investigations
- cervical cytology by Pap test
  - koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
- anogenital warts
  - patient administered
    - podofilox 0.5% solution or gel BID x 3 d in a row (4 d off) then repeat x 4 wk
    - imiquimod (Aldara®) 5% cream 3x/wk nightly x 16 wk
    - sinecatechins 10% ointment 0.5 cm strand TID x up to 16 wk, daily dose ≤ 250 mg (need not be washed off)
  - provider administered
    - cryotherapy with liquid nitrogen: repeat q1-2 wk
    - podophyllin resin in tincture of benzoin: weekly
    - trichloroacetic acid (TCA) (80-90%) or bichloroacetic acid weekly x 4-6 wk; safe in pregnancy
    - surgical removal/laser
- intraepithelial lesions and cancers (See *Gynecological Oncology, GY42*)

Genital Warts During Pregnancy
- Condyloma tend to get larger in pregnancy and should be treated early (consider excision)
- Remove only if obstructing birth canal or risk of extensive bleeding
- Do not use imiquimod, podophyllin, or podofilox in pregnancy
- Baby at risk for juvenile respiratory papillomatosis, but condyloma dissection does not significantly reduce the risk

Human Rights in Health Equity: Cervical Cancer and HPV Vaccines
Am J Law Med 2009;35:365-387
- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer.
- In most developing countries cervical cancer rates have risen or remained unchanged.
- It must be recognized that cervical cancer disparities between race groups, urban and rural residence, and high and low socioeconomic status are attributed to disparate screening and vaccination coverage.
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited healthcare settings, sexual health stigma, and related privacy concerns.

A 9-Valent HPV Vaccine Against Infection and Intraepithelial Neoplasia in Women
NEJM 2015;372:711-723
Purpose: To determine the efficacy and immunogenicity of the qHPV (types 6, 11, 16, 18) vs. 9vHPV (five additional types 31, 33, 45, 52, 58) vaccines.
Method: International randomized, double-blinded phase 2B-3 study of 9vHPV vaccine in 14215 women between ages of 16-26. Participants were randomized to the 9vHPV vaccine group or the qHPV vaccine group and each received a series of three IM injections (d 1, 2 mo, and 6 mo). Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue was obtained and used for HPV DNA testing/Pap smear.
Results: Rate of high-grade cervical, vulvar, or vaginal disease was 14.0 per 1000 person-yr in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 was 0.1 per 1000 person-yr in the 9vHPV group and 1.6 per 1000 person-yr in the qHPV group (95% CI=80.9-99.8). Antibody responses to HPV-6, 11, 16, and 18 were not significantly different between the two vaccine groups although adverse events related to injection sites were more common in the 9vHPV group.
Conclusions: The 9vHPV vaccine was non-inferior to qHPV vaccine in preventing infection and disease related to HPV-6, 11, 16, and 18 and also covered additional oncogenic types HPV-31, 33, 45, 52, and 58 in a susceptible population.

Prevention
- vaccination: Gardasil®9, Gardasil®, Cervarix® (see *Table 28, GY49*)
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

HERPES SIMPLEX VIRUS OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: average incubation is 4 d after exposure (range 2-12 d)
- prodromal symptoms: tingling, burning, and pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: common but less severe, less frequent, and shorter in duration (usually only HSV-2)

Investigations
- viral culture preferred in patients with ulcer present; however, decreased sensitivity as lesions heal
- HSV DNA PCR
- cytologic smear (Tzanck smear) shows multinucleated giant cells, limited use due to low sensitivity and specificity
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not routinely available in Canada)

Treatment
- first episode: acyclovir 200 mg PO five times daily x 7-10 d, famciclovir 250 mg PO TID x 7-10 d, or valacyclovir 1 g PO BID x 7-10 d
- recurrent episode: acyclovir 400 mg PO TID x 5 d, famciclovir 125 mg PO BID x 5 d, or valacyclovir 1 g PO once daily x 5 d
- daily suppressive therapy
  - consider for >6 recurrences per yr or recurrence every 2 mo
  - acyclovir 400 mg PO BID, famciclovir 250 mg PO BID, valacyclovir 500 mg PO once daily, or valacyclovir 1 g PO once daily
- severe disease: IV acyclovir 5-10 mg/kg q8 h x 2-7 d or until clinical improvement observed followed by oral antiviral therapy to complete 10 d of total therapy
- education regarding transmission: avoid sexual contact from onset of prodrome until lesions have cleared, use barrier contraception

SYPHILIS

Etiology
- *Treponema pallidum*

Classifications
- primary syphilis
  - 3-4 wk after exposure (median incubation 21 d)
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection, in 25% of patients with untreated primary syphilis
  - nonspecific symptoms: malaise, anorexia, headache, and diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, and limbs
  - condylomata lata: anogenital, broad-based, fleshy, grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis and general paresis
  - cardiovascular: aortic aneurysm and dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate, and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

Epidemiology of Genital Ulcers

HSV	70-80%
1° Syphilis	5%
Chancroid *(Haemophilus ducreyi)*	<1%

Investigations
- aspiration of ulcer serum or node
- dark field microscopy (most sensitive and specific diagnostic test for syphilis): look for spirochetes
- non-treponemal screening tests (VDRL, RPR); non-reactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment
- reportable disease, partners should be referred for treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
- treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1 wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units q4 h x 10-14 d
- screening
  - high-risk groups (partner with syphilis, HIV-infected individuals, high risk sexual behaviour, history of incarceration)
  - in pregnancy (see Obstetrics, *Infections During Pregnancy, OB32*)

Complications
- if untreated, 25-40% will experience late complications

HIV
- see Infectious Diseases, ID27

Bartholin Gland Abscess

Etiology
- follows the infection of an obstructed Bartholin duct
- most commonly *E. coli*, polymicrobial, *S. aureus*, and Group B *Strep*

Clinical Features
- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

Treatment
- large mass >3 cm
  - 1st or 2nd episode: I&D under local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
  - recurrence after two failed attempts with Word catheter: marsupialization in ER under sedation, or under GA
- small mass <3 cm
  - I&D with Word catheter, sitz baths, warm compresses
- antibiotics: reserved for patients with recurrence, high risk of complicated infection, culture-positive MRSA, systemic infection

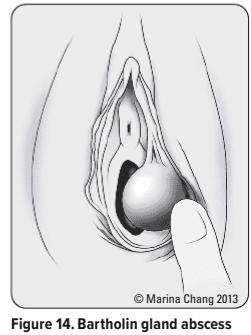


Figure 14. Bartholin gland abscess

Pelvic Inflammatory Disease

- infection of the upper genital tract (above the cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum ± contiguous structures that primarily affects young, sexually active women

PID accounts for up to 20% of all gynecological hospital admissions

Etiology
- microbial etiology unknown in most cases, often considered a polymicrobial infection
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
    - gonorrhea and chlamydia often co-exist
  - *M. genitalium*
  - *E. coli* and colonic anaerobes found in rare cases of PID in postmenopausal women
  - very rare pathogens: *M. tuberculosis, H. influenzae, S. pneumoniae*, and the agents of actinomycosis

Risk Factors
- age 15-25 yr
- multiple partners, STI in partner
- previous PID
- IUD (extremely rare, occurs within first 3 wk after insertion)

PID Diagnosis

Minimum diagnostic criteria
- Cervical motion tenderness
- Uterine tenderness
- Adnexal tenderness

Additional diagnostic criteria
- Oral temperature >38.3°C
- Leukocytosis on saline microscopy of vaginal secretions/wet mount
- Elevated ESR or CRP
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

Definitive diagnostic criteria
- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal sonography or MRI showing thickened fluid-filled tubes, free fluid or tubo-ovarian complex
- Gold standard: laparoscopy demonstrating abnormalities consistent with PID

Clinical Features
- wide spectrum of clinical presentation: time course typically acute although many patients will have subclinical PID that does not prompt a patient to present for medical care but severe enough to cause significant sequelae (fertility issues)
- clinical diagnosis of PID: fever >38.3°C, lower abdominal pain and tenderness, and abnormal discharge (cervical or vaginal)
- uncommon: N/V, dysuria, and AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

Investigations
- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine routine and microscopy (R&M)
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - nucleic acid amplification tests (NAAT) for *N. gonorrhoeae, C. trachomatis, M. genitalium*
  - HIV testing and serologic testing for syphilis
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy
  - only done in patients that have failed outpatient treatment, symptoms not improving after 72 h of inpatient treatment, or unclear diagnosis
  - surgery has high specificity but low sensitivity

Treatment
- must treat with polymicrobial coverage
- percutaneous drainage of abscess under U/S guidance
- laparoscopic drainage when no response to treatment, surgical (salpingectomy, TAH/BSO) if failure
- consider removing IUD after a minimum of 24 h of treatment
- reportable disease, treat partners
- consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection

Table 16. Inpatient and Outpatient Management Options for Pelvic Inflammatory Disease

	Inpatient	Outpatient
Indications	Moderate to severe illness Atypical infection Adnexal mass, tubo-ovarian mass, or pelvic abscess Failed or cannot tolerate oral therapy Immunocompromised Pregnant Adolescent (first episode) Surgical emergency cannot be excluded (e.g. ovarian torsion) PID is secondary to instrumentation	Typical findings Mild to moderate illness Oral antibiotics tolerated Compliance ensured Follow up within 48-72 h (to ensure symptoms not worsening)
Antibiotic Regimen	Cefoxitin 2 g IV q6 h + doxycycline 100 mg PO/IV q12 h or Clindamycin 900 mg IV q8 h + gentamycin 2 mg/kg IV/IM loading dose then gentamicin/tobramicin 1.5 mg/kg q8 h maintenance dose Continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO BID to complete 14 d (add metronidazole 500 mg PO BID x 14 d in patients with tubo-ovarian abscess)	1st line: ceftriaxone 500 mg IM x 1 dose + doxycycline 100 mg PO BID x 14 d or cefoxitin 2 g IM x 1 dose + probenecid 1 g PO + doxycycline 100 mg PO BID ± metronidazole 500 mg PO BID x 14 d 2nd line: ofloxacin 400 mg PO BID x 14 d or levofloxacin 500 mg PO once daily x 14 d ± metronidazole 500 mg PO BID x 14 d

Complications of Untreated Pelvic Inflammatory Disease

- chronic pelvic pain
- persistent hydrosalpinx
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID: 13% infertility
  - 2 episodes of PID: 36% infertility
- bacteremia
- septic arthritis, endocarditis

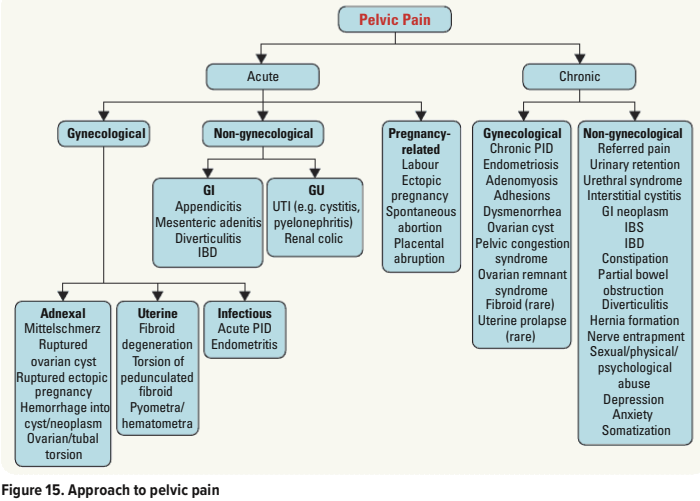


Figure 15. Approach to pelvic pain

Toxic Shock Syndrome (TSS)

- see Infectious Diseases, ID22
- Staphylococcal toxic shock syndrome (TSS) is a clinical illness characterized by rapid onset of fever, rash, hypotension, and multiorgan system involvement

Toxic Shock Syndrome
Multiple organ system failure due to *S. aureus* exotoxin (rare condition)

Risk Factors

- menstrual TSS
  - significantly decreased as a result of the withdrawal of highly-absorbent tampons and polyacrylate rayon-containing products from the market; however, tampon use remains a risk factor for TSS (high absorbency, tampons used continuously for more days of their cycle, and keeping a single tampon in place for a longer period of time)

- non-menstrual TSS (gynecologic)
  - diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
  - surgical and postpartum wound infections, mastitis, sinusitis, osteomyelitis, arthritis, burns, cutaneous lesions, etc.

Clinical Features
- sudden high fever/chills
- sore throat, headache, and diarrhea
- macular erythroderma followed by desquamation 1-2 wk later
- signs of multisystem organ failure
- refractory hypotension

Treatment
- treatment of shock
- remove potential sources of infection (foreign objects)
- surgical debridement (if warranted)
- adequate hydration
- empiric antibiotic therapy with vancomycin (load 20-35 mg/kg and maintenance 15-20 mg/kg q8-12 h) + clindamycin 900 mg IV q8 h + piperacillin-tazobactam 4.5 g IV q6 h
- continue combination therapy until patient is hemodynamically stable for at least 48-72 h

Surgical Infections

Postoperative Infections in Gynecological Surgery
- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, and discharge involving vaginal cuff
  - if fever and leukocytosis, treat with broad-spectrum ABx (i.e. clindamycin and gentamicin)
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see General and Thoracic Surgery, *Postoperative Fever, GS8*

Sexual Abuse

- see Emergency Medicine, ER27 and Family Medicine, FM46

Sexuality and Sexual Dysfunction

SEXUAL RESPONSE
1. desire: energy that allows an individual to initiate or respond to sexual stimulation (libido)
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement (excitement)
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

Note: this framework cannot be applied consistently to a patient's sexual response. For many patients, the phases may vary in sequence, overlap, repeat, or be absent during some or all sexual encounters

SEXUAL DYSFUNCTION

Classification
- lack of desire (most common)
- lack of arousal
- anorgasmia
  - primary anorgasmia: never achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but unable to achieve orgasms presently
- dyspareunia: painful intercourse, can be superficial or deep

Etiology
- biological:
  - gynecological (e.g. pregnancy, childbirth, menopausal atrophy, endometriosis, prolapse, urinary incontinence)
  - urological (e.g. recurrent UTI, chronic renal failure)
  - vascular (e.g. peripheral vascular disease, CAD)
  - neurological dysfunction (e.g. nerve entrapment syndrome, spinal cord injury, multiple sclerosis, Parkinson's)

  - musculoskeletal (e.g. arthritis, mechanical back pain)
  - systemic health disorders (e.g. DM, thyroid disorders)
  - medication side effects (e.g. β-blockers, benzodiazepines, SSRIs, antipsychotics, oral contraceptives)
  - behavioural or lifestyle (e.g. smoking, alcohol consumption, opioids, obesity)
- psychological:
  - early events: history of sexual violence, unpleasant early sexual experiences, or growing up in a family or society that communicates no information or negative messages about female sexuality
  - current events: depression, anxiety, psychosis, fatigue, stress, or other mental health disorders
- relationship:
  - abuse
  - relationship distress
  - failure to engage in effective sexual stimulation

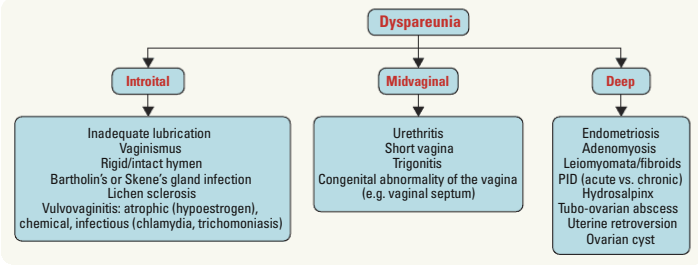


Figure 16. Approach to dyspareunia

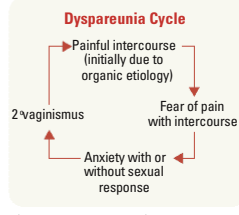

Dyspareunia Cycle
Painful intercourse (initially due to organic etiology)
Fear of pain with intercourse
Anxiety with or without sexual response
2° vaginismus

Figure 17. Dyspareunia cycle

Treatment

- general:
  - assess patient goals and construct a safety plan as needed
  - counselling
  - lifestyle changes
  - improve body image
- lack of desire:
  - biological: rule out other conditions/medication side effects; consider sildenafil for SSRI side effects; consider androgens (testosterone, DHEA), estrogens, tibolone in postmenopausal women; consider serotonergic and dopaminergic agents: flibanserin, bupropion, buspirone; consider bremelanotide
  - psychological: rule out/treat depression, other mental health issues
  - relationship: assess couple interaction and partner sexual function; treat partner and relationship conflict
- concerns with arousal/lubrication:
  - biological: non-hormonal, water-based lubricants; consider estrogen (topical cream, tablet, or ring) or coconut oil
  - psychological: address sexual anxieties
  - relationship: education regarding slowing of sexual response with aging
- anorgasmia:
  - biological: augment stimulation ± vibrator; consider androgens
  - psychological: sex education, anxiety reduction, and use of erotica
  - relationship: stimulation needs and helping patient teach partner what they need
- sexual pain disorders:
  - biological: rule out other conditions; topical estrogen if atrophy; consider nerve modulators (amitriptyline, gabapentin, or pregabalin); pelvic floor physiotherapy
  - psychological: sex therapy if vaginismus
  - relationship: rule out abuse (with patient alone)

Menopause

• see Family Medicine, FM43

Definitions

• lack of menses for 1 yr
• timing of menopause
  ▪ physiological; average age 51 yr (follicular atresia)
  ▪ premature ovarian insufficiency; before age 40 (autoimmune disorder, infection, Turner's syndrome)
  ▪ iatrogenic (surgical/radiation/chemotherapy)

Clinical Features

• associated with estrogen deficiency
  ▪ vasomotor instability (tends to dissipate with time)
    ◆ hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, and palpitations
  ▪ urogenital atrophy involving vagina, urethra, and bladder (genitourinary syndrome of menopause (GUSM))
    ◆ dyspareunia, pruritus, vaginal dryness, bleeding, post-coital bleeding, urinary frequency, urgency, and incontinence
    ◆ inspection may reveal: thinning of tissues, erythema, petechiae, abrasions, and dryness on speculum exam
  ▪ skeletal
    ◆ osteoporosis, joint and muscle pain, and back pain
  ▪ skin and soft tissue
    ◆ decreased breast size, and skin thinning/loss of elasticity
  ▪ psychological
    ◆ increased anxiety, depression, irritability, fatigue, decreased libido, and memory loss

Investigations

• for women with irregular cycles and menopausal symptoms:
  ▪ >45 yr: no testing necessary
  ▪ 40-45 yr: β-hCG, prolactin, TSH
  ▪ <40 yr: β-hCG, FSH, prolactin, TSH
• increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
• FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
• decreased levels of estradiol (later)

Treatment

• goal is for individual symptom management

Table 17. Treatment of Menopause

Vasomotor Instability	Vaginal Atrophy	Urogenital Health	Osteoporosis	Decreased Libido	CVD*	Mood and Memory
Menopause hormonal therapy (MHT) as first line, SSRI, venlafaxine, gabapentin, propanolol, clonidine, acupuncture, behavioural modifications	Local estrogen: cream (Premarin® or Estragyn Vaginal Cream®), vaginal suppository (VagiFem®), ring (Estring®), lubricants (Replens®), intravaginal laser	Lifestyle changes (weight loss, bladder training), pelvic floor exercises, local estrogen replacement, surgery	Calcium 1000-1500 mg once daily, vitamin D 800-1000 IU, weight-bearing exercise, smoking cessation, bisphosphonates (e.g. alendronate), SERMs (e.g. raloxifene (Evista®)), HRT (second-line treatment)	Vaginal lubricants, counselling, androgen-replacement testosterone cream or the oral form (Andriol®)	Manage CVD risk factors	Anti-depressants (first line), MHT (augments effect), CBT

*CVD (cardiovascular disease)

Menopause
Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins)

"Being in menopause"
Lack of menses for 1 yr

Perimenopause
Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset

Menopause Pathophysiology

Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)
↓
Less estrogen is produced
↓
Decreased negative feedback on hypothalamic-pituitary-adrenal axis
↓
Increased FSH and LH
↓
Stromal cells continue to produce androgens as a result of increased LH stimulation

Figure 18. Menopause pathophysiology

85% of women experience hot flashes
20-30% seek medical attention
10% are unable to work

Menopause Hormone Therapy

- see Family Medicine, FM43

Treatment Guidelines

- primary indication is treatment of menopausal symptoms (vasomotor instability)
  - should not be prescribed if the only objective is the prevention of chronic disease
- before starting, review the benefits and risks (see *Table 18*) and contraindications with the patient
- use the lowest effective dose; patients with standard dose should be advised to lower dose after a few years
- patients receiving MHT must be evaluated annually
- decisions around duration of treatment should be individualized, but recommended to avoid treatment >5 yr with combination estrogen and progesterone treatment due to the duration-dependent risk of breast cancer
  - tapering and abruptly discontinuing MHT have similar impact on symptom recurrence, but for patients with a history of severe baseline vasomotor symptom, gradual tapering is probably preferable

Table 18. MHT Benefits vs. Risks

Benefits	Risks
Reduction of vasomotor symptoms Reduction of sleep problems Reduction of mood or anxiety problems Reduction of aches and pains Osteoporosis prevention and treatment Reversal of vulvar and vaginal atrophy (local estrogen therapy recommended if such atrophy is the only indication for therapy)	Thromboembolic events Stroke Breast cancer (increased risk after 4-5 yr with estrogen-progesterone regimens, no increased risk for at least 8 yr with estrogen-alone and no uterus regimens) Coronary heart disease (for women age >60 and those who are >10 yr after menopause) Endometrial hyperplasia and cancer (with estrogen-only regimens and uterus *in situ*)

MHT Components

- estrogen
  - oral or transdermal (e.g. patch, gel)
  - transdermal preferred for patients overall, especially with hypertriglyceridemia or impaired hepatic function, smokers, and patients low-dose (preferred dose: Premarin® 0.3 mg/Estradot® patch 25 µg, can increase if necessary)
- progestin
  - given in combination with estrogen for patients with an intact uterus to prevent development of endometrial hyperplasia/cancer

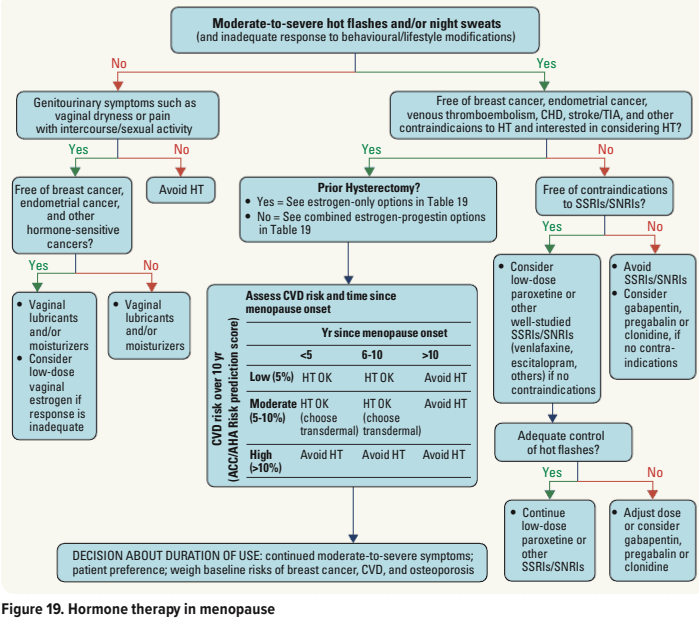

Moderate-to-severe hot flashes and/or night sweats
(and inadequate response to behavioural/lifestyle modifications)
No
Yes
Genitourinary symptoms such as vaginal dryness or pain with intercourse/sexual activity
Free of breast cancer, endometrial cancer, venous thromboembolism, CHD, stroke/TIA, and other contraindicaions to HT and interested in considering HT?
Yes
No
Yes
No
Free of breast cancer, endometrial cancer, and other hormone-sensitive cancers?
Avoid HT
Prior Hysterectomy?
• Yes = See estrogen-only options in Table 19
• No = See combined estrogen-progestin options in Table 19
Free of contraindications to SSRIs/SNRIs?
Yes
No
Yes
No
• Vaginal lubricants and/or moisturizers
• Consider low-dose vaginal estrogen if response is inadequate
• Vaginal lubricants and/or moisturizers
Assess CVD risk and time since menopause onset
CVD risk over 10 yr (ACC/AHA Risk prediction score)
Yr since menopause onset
<5
6-10
>10
Low (5%) HT OK HT OK Avoid HT
Moderate (5-10%) HT OK (choose transdermal) HT OK (choose transdermal) Avoid HT
High (>10%) Avoid HT Avoid HT Avoid HT
• Consider low-dose paroxetine or other well-studied SSRIs/SNRIs (venlafaxine, escitalopram, others) if no contraindications
• Avoid SSRIs/SNRIs
• Consider gabapentin, pregabalin or clonidine, if no contra-indications
Adequate control of hot flashes?
Yes
No
• Continue low-dose paroxetine or other SSRIs/SNRIs
• Adjust dose or consider gabapentin, pregabalin or clonidine
DECISION ABOUT DURATION OF USE: continued moderate-to-severe symptoms; patient preference; weigh baseline risks of breast cancer, CVD, and osteoporosis

Figure 19. Hormone therapy in menopause

Long-Term Hormone Therapy for Perimenopausal and Postmenopausal Women
Cochrane DB Syst Rev 2017;1:CD004143
Purpose: To determine the effect of long-term HT (hormone therapy) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition, and quality of life (QOL) in perimenopausal and postmenopausal women, during HT use, and after cessation of HT.
Results: 22 studies with 43637 women included. Most studies included postmenopausal American women with at least some degree of comorbidity, with a mean participant age over 60 yr. Combined continuous HT: increased risk of coronary event after 1 yr (from 2/1000 to 3-7/1000), venous thromboembolism after 1 yr (2/1000 to 4-11/1000), stroke after 3 yr (6/1000 to 6-12/1000), breast cancer after 5.6 yr (19/1000 to 20-30/1000), gallbladder disease after 5.6 yr (27/1000 to 38-60/1000), and death from lung cancer after 5.6 yr use plus 2.4 yr additional follow up (5/1000 to 6-13/1000). Estrogen only HT: increased risk of venous thromboembolism after 1-2 yr use (2/1000 to 2-10/1000; after 7 yr, 16/1000 to 16-28/1000), stroke after 7 yr (24/1000 to 25-40/1000), and gallbladder disease after 7 yr use (27/1000 to 38-60/1000) but reduced the risk of breast cancer after 7yr (25/1000 to 15-25/1000 and clinical fracture after 7yr (141/1000 to 92-113/1000). Women >65 yr of age taking combined HT had shown an increase in the incidence of dementia after 4 yr use (9/1000 to 11-30/1000). For women with cardiovascular disease, use of combined continuous HT significantly increased the risk of venous thromboembolism at 1 yr (3/1000 to 3-29/1000).
Conclusions: HT may be contraindicated for some women with increased risk of cardiovascular disease, thromboembolic disease, and certain cancers such as breast cancer in women with a uterus. HT is not indicated for primary or secondary prevention of cardiovascular disease, dementia, or deterioration of cognitive function.

Osteoporosis is the single most important health hazard associated with menopause

Cardiovascular disease is the leading cause of death post-menopause

Increased risk of breast cancer (RR 1.3) is associated with estrogen+progesterone HRT, but not with estrogen-only HRT

All women taking HRT should have periodic surveillance and counselling regarding its benefits and risks

Table 19. Examples of MHT Regimens

MHT Regimen	Trade Names	Standard Doses
Estrogen-only – oral	Estrace®	17 β-estradiol 0.5-1 mg tablet daily
	Premarin®	CE 0.3-0.625 mg tablet daily
	Estragyn®	Esterified estrogens 0.3-0.625 mg cyclic
Estrogen-only – transdermal	Patches:	
	Estradot®, Sandoz Estradiol Derm®, Oesclim®, Climara®	17 β-estradiol 25-100 µg 1-2x/wk
	Gel:	
	Estrogel®	1-2 metered doses/actuation daily
	Divigel®	0.25-1 mg packets daily
Estrogen-only – vaginal	Cream:	
	Premarin®	CE 0.625 mg/g
	Estragyn®	Estrone 1 mg/g
	Inserts: Vagifem®	17 β-estradiol 10 µg
	Ring: Estring®	17 β-estradiol 2 mg
Combined E-P – oral	Activelle®	1 mg 17 β-estradiol/0.5 mg NEA
	Angeliq®	1 mg 17 β-estradiol/1 mg drospirenone
Combined E-P – transdermal	Patch: Estalis® (2 doses available)	17 β-estradiol/NEA: 50/140 mµg continuous 2x/wk 50/140 mµg or 50/250 mµg cyclic 2x/wk

CE = conjugated estrogen; E-P = estrogen-progestin; NEA = norethindrone acetate
Current common practice includes using the Mirena® IUD as the progesterone component (levonorgestrel 52 mg over 5 yr, approximately 20 µg/d)

Side Effects of MHT

- estrogen
  - breast tenderness
  - nausea
  - headache
  - bloating
- progestins
  - mood alterations
  - breast tenderness
  - bloating
  - sedation (micronized progesterone)

Contraindications to MHT

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - history of breast cancer
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis, or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - DM (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, and impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials
JAMA 2013;310:1353-1368
Purpose: To report comprehensive findings from the 2 Women's Health Initiative (WHI) hormone therapy trials with extended post-intervention follow-up.
Methods: A total of 27347 postmenopausal women ages 50-79 were enrolled at 40 US centers. In the CEE+MPA trial, 16608 women, with intact uterus, received either continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg once daily) or placebo. In the CEE-only trial, 10739 women, with prior hysterectomy, received either CEE 0.625 mg once daily or placebo.
Results: Results all reported as difference between treatment and placebo in cases per 100000 person-yr, stratified by age.

	CEE + MPA trial		CEE alone trial	
CHD	50-59	5	50-59	-11
	60-69	0	60-69	-3
	70-79	19	70-79	7
Invasive breast cancer	50-59	6	50-59	-5
	60-69	8	60-69	-10
	70-79	15	70-79	-5
Stroke	50-59	5	50-59	-1
	60-69	11	60-69	18
	70-79	13	70-79	17
PE	50-59	6	50-59	3
	60-69	8	60-69	7
	70-79	18	70-79	-2
Colorectal cancer	50-59	-1	50-59	-3
	60-69	-8	60-69	-2
	70-79	-11	70-79	19
Hip fracture	50-59	-3	50-59	3
	60-69	-4	60-69	-6
	70-79	-14	70-79	-21

Absolute Contraindications to MHT

ABCD
Acute liver disease
Undiagnosed vaginal Bleeding
Cancer (breast/uterine), Cardiovascular disease
DVT (thromboembolic disease)

Urogynecology

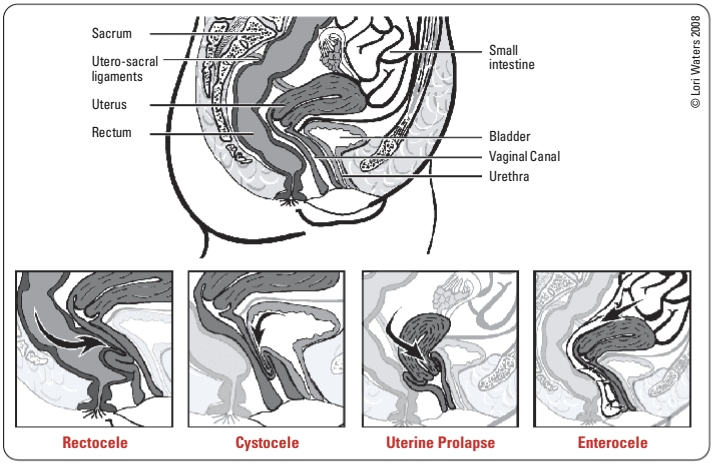


Figure 20. Pelvic anatomy

Pelvic Organ Prolapse

Etiology

- related to:
  - vaginal childbirth
  - aging
  - decreased estrogen (post-menopause)
  - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  - ethnicity (greater incidence in White women > Asian or African women)
  - connective tissue disorders

Pelvic Organ Prolapse
A weakening in the structures of the pelvic floor resulting in descent of one or more of the pelvic structures (bladder/rectum/small intestine/uterus) into the vagina

Diagnosis

- medical history
  - assess symptoms specific to prolapse: pressure, bulge
  - assess urinary, defecatory, and sexual concerns, which are often associated with pelvic organ prolapse
- physical exam (each component with patient relaxed and then while straining)
  - inspection in the dorsal lithotomy position
  - evaluate for apical prolapse with a bivalve speculum exam, then evaluate for anterior and posterior prolapse with the posterior blade of the bivalve speculum
  - use the POP-Q staging system to quantify stage of prolapse
  - evaluate for any coexisting pelvic abnormalities with a bimanual exam
  - test the strength of pelvic floor muscles with voluntary Kegel contractions
- ancillary studies
  - if continent with apical prolapse, consider clinical or urodynamic testing with and without reduction of prolapse to investigate for occult stress urinary incontinence
  - if voiding symptoms, consider post-void residual volume to evaluate urinary retention
  - if urgency or other UTI symptoms, consider urine microscopy and culture to test for UTI

POP-Q Staging of Pelvic Organ Prolapse
0 = no prolapse
1 = most distal portion of prolapse >1 cm above level of hymen
2 = most distal portion of prolapse is between 1 cm above or below the hymen
3 = most distal portion of prolapse >1 cm below level of hymen but no further than 2 cm less than the total vaginal length
4 = complete procidentia (uterus present with complete herniation of anterior, posterior, and apical compartments) or vault eversion (no uterus present with complete eversion of the anterior, posterior, and apical compartments), most distal prolapse protrudes 2 cm of total vaginal length

GENERAL CONSERVATIVE TREATMENT

- weight loss
- pelvic floor muscle training (e.g. Kegel exercises, pelvic physiotherapy)
- local vaginal estrogen therapy
- vaginal pessary (intravaginal devices that are either supportive or space-occupying)

The primary clinical features of pelvic organ prolapse are vaginal bulge and pressure

Table 20. Types and Management of Pelvic Organ Prolapse

Type	Clinical Features	Treatment
Anterior Vaginal Wall Prolapse (previously "cystocele") (protrusion of bladder into the anterior vaginal wall)	Frequency, urgency, nocturia Stress incontinence Incomplete bladder emptying ± associated increased incidence of UTIs (may lead to renal impairment)	General conservative treatment (see above) Anterior colporrhaphy ("anterior repair") Consider additional/alternative surgical procedure if documented urinary stress incontinence Can consider pessary
Posterior Vaginal Wall Prolapse (previously "rectocele") (protrusion of rectum into posterior vaginal wall)	Straining/digitation to evacuate stool Constipation	General conservative treatment (see above) Also laxatives and stool softeners Posterior colporrhaphy ("posterior repair"), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)
Uterine Prolapse (protrusion of cervix and uterus into vagina)	A type of apical prolapse Groin/back pain (stretching of uterosacral ligaments) Feeling of heaviness/pressure in the pelvis Worse with standing, lifting Worse at the end of the day Relieved by lying down Ulceration/bleeding (particularly if hypoestrogenic) ± urinary incontinence	General conservative treatment (see above) Vaginal hysterectomy ± surgical prevention of vault prolapse Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present Can consider pessary
Vault Prolapse (previously "enterocele", protrusion of apex of vaginal vault into vagina, post-hysterectomy, often containing small bowel)	A type of apical prolapse Same as uterine prolapse	General conservative treatment (see above) Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension

Surgery: native tissue repair vs. mesh reconstruction (usually reserved for severe, recurrent prolapse)

The only **true** hernia of the pelvis is an ENTEROCELE because peritoneum herniates with the small bowel

Kegel Exercises
Regular contraction and relaxation to strengthen pelvic floor muscles

Reverse Kegel Exercises
1 s contraction then 5 s of relaxation

Urinary Incontinence

- see Urology, U6

STRESS INCONTINENCE

Definition
- involuntary loss of urine with increased intra-abdominal pressure (cough, laugh, sneeze, walk, run)
- affects 4-35% of all women

Risk Factors for Stress Incontinence in Women
- increased age
- obesity
- pregnancy/vaginal delivery
- hypoestrogenic state (post-menopause)
- smoking/chronic cough
- neurological
- genetics
- high impact exercise

Diagnosis
- history
  - onset, frequency, severity, and pattern of urinary incontinence
  - frequency, dysuria, urgency, and nocturia
  - pads used per 24 h
  - obstructive urinary symptoms (incomplete voiding, hesitancy, straining, post-void dribbling, and recurrent UTI)
  - pelvic organ prolapse symptoms
  - neurological conditions/symptoms
  - obstetric history, and current menopause/hormone therapy status
  - medications (sedatives, diuretics, anticholinergic medications, and OTCs)
  - lifestyle risk factors (caffeine, smoking, weight, exercise, and occupation)
  - urinary diary
- physical exam
  - height, weight, and BMI
  - abdominal exam: scars, abdominal mass, and presence of a full bladder
  - neurological exam: S2-S4 sacral nerves (motor, sensory, and reflexes)
  - elderly: mini mental status exam, and observe mobility
  - pelvic exam: inspect vulva and urogenital epithelium, assess for signs of pelvic organ prolapse, and digital rectal exam to assess for anal sphincter tone and perineal sensation
  - standing stress test

- studies
  - urinalysis: hematuria, pyuria, glucosuria, proteinuria
    - hematuria/irritative voiding symptoms: cytology
    - pyuria/bacteria: urine culture
  - post-void residual
    - normal: ≤1/3 total volume
    - abnormal: >1/3 total volume (poor bladder contractility or bladder outlet obstruction)
  - urodynamic testing

Treatment
- for conservative management, see *Pelvic Organ Prolapse, GY39*
- procedures: vaginal laser, urethral bulking
- surgical
  - midurethral sling (TVT, TOT)
  - urethropexy (Burch procedure)
  - pubovaginal sling
  - urethral bulking

OVERACTIVE BLADDER

Definition
- symptom syndrome defined as "urgency, with or without urge urinary incontinence (UUI), usually with frequency and nocturia"
- 16% of all patients
- UUI: involuntary leakage with or immediately preceded by a strong desire to void
  - involuntary bladder contraction that overcomes the urethral sphincter mechanism OR
  - poor bladder compliance

Etiology
- idiopathic: congenital and aging
- medical: CHF, DM, and diuretics
- neurogenic: multiple sclerosis, Parkinson's, CVD, dementia, and spinal cord injury
- bladder outlet obstruction: previous bladder neck surgery and pelvic organ prolapse
- gynecologic: UTI, pregnancy, pelvic mass, and urethral diverticulum
- psychosomatic: habits, anxiety, and high fluid consumption

Diagnosis
- see *Stress Incontinence, GY40* for diagnosis

Treatment
- behaviour modification (reduce bladder irritants (caffeine, smoking, alcohol, acidic, spicy); adequate water intake; regular voiding schedule)
- bladder training with pelvic physiotherapist
- medications
  - anticholinergics
    - oxybutynin (oral: Ditropan®; patch: Oxytrol®; transdermal gel: Gelnique®)
    - tolterodine (Detrol®)
    - fesoterodine (Toviaz®)
    - solifenacin (Vesicare®)
    - trospium (Trosec®)
    - darifenacin (Enablex®)
  - β-adrenergic agonist: mirabegron (Myrbetriq®)
- procedures: sacral neuromodulation, detrusor botox injection

Gynecological Oncology

Pelvic Mass

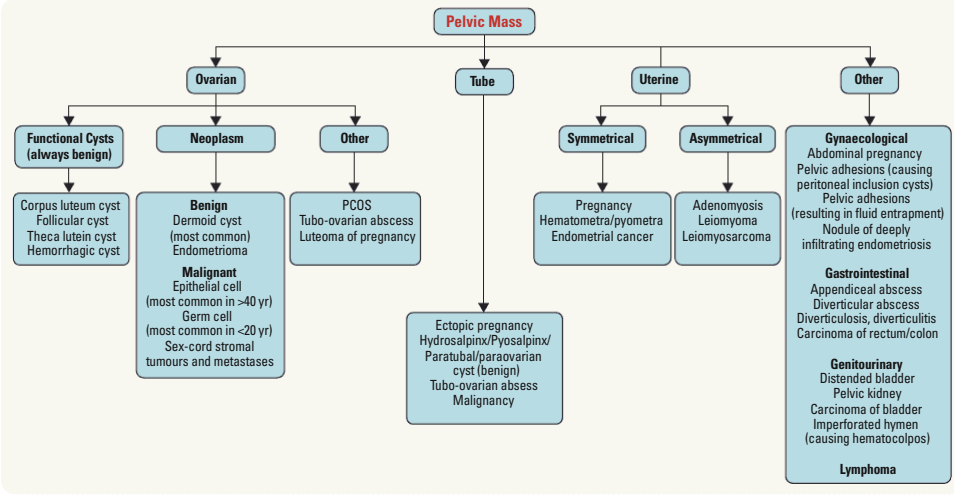


Figure 21. Differential diagnosis of pelvic mass

Uterus

ENDOMETRIAL CARCINOMA

Epidemiology

- most common gynaecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of patients with a uterus develop endometrial carcinoma during their lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5 yr survival for stage I disease
- 70-80% 5 yr survival for all stages

Table 21. Features of Type I and Type II Endometrial Cancer

	Type I	Type II
Description	Estrogen-related (i.e. excess/unopposed estrogen): Endometrioid Includes well-differentiated (grade 1 and 2) endometrioid adenocarcinoma 80% of cases	Non-estrogen related: Non-endometrioid Includes serous, clear cell, grade 4 endometrioid and undifferentiated carcinomas, carcinosarcoma 20% of cases, poorer prognosis
Risk Factors (Increasing age and family history are risk factors for both types)	PCOS Diabetes mellitus Unbalanced HRT (balanced HRT is protective) Nulliparity or history of infertility related to anovulation Late menopause (>55 yr), early menarche Estrogen-producing ovarian tumours (e.g. granulosa cell tumours) HNPCC*/Lynch II syndrome Tamoxifen Prior pelvic radiation	Parous people More likely in Black patients Associated with p53 mutation, HER2 overexpression
Clinical Features	Postmenopausal bleeding AUB in premenopausal patients (menorrhagia, intermenstrual bleeding)	AUB

*HNPCC = Hereditary non-polyposis colorectal cancer

Incidence of Malignant Gynecological Lesions in North America
endometrium > ovary > cervix > vulva > vagina > fallopian tube

Risk Factors for Endometrial Cancer

COLD NUT
Cancer (ovarian, breast, colon)
Obesity
Late menopause
Diabetes mellitus
Nulliparity
Unopposed estrogen: PCOS, anovulation, HRT
Tamoxifen (chronic use)
(Genetic syndromes: Hereditary Nonpolyposis Colorectal Cancer (HNPCC) - Lynch II syndrome, Cowden syndrome)

Postmenopausal bleeding = endometrial cancer until proven otherwise (95% present with vaginal bleeding)

An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding and a thickness of more than 11 mm is considered abnormal in a postmenopausal woman without vaginal bleeding

Screening
- no known benefit for mass screening
- annual endometrial sampling starting at age 30-35 only for patients at high risk (HNPCC/Lynch II syndrome)
- routine pelvic ultrasound should not be used as a screening test (high false positive rates)

Investigations
- endometrial sampling in all suspected patients (office endometrial biopsy most commonly)
- hysteroscopy considered in patients with persistent uterine bleeding with benign sampling or inadequate sampling
- additional tumour markers, CT, MRI only in specific cases, such as high-grade tumours or suspected extrauterine spread

Table 22. FIGO Staging of Endometrial Cancer (2009)

Stage	Description	Stage	Description
I	Confined to corpus uteri including endocervical glandular involvement	IIIC	Metastasis to pelvic ± para-aortic LNs
IA	Less than 50% myometrial invasion	IIIC1	Positive pelvic LN
IB	More than 50% myometrial invasion	IIIC2	Positive para-aortic LN ± positive pelvic LNs
II	Invades cervical stroma, but does not extend beyond uterus	IV	Invades bladder ± bowel mucosa ± distant metastases (note: omental disease is stage IV)
III	Involves serosa, adnexa, vagina, or parametrium	IVA	Invades bladder ± bowel mucosa
IIIA	Invasion of serosa ± adnexae	IVB	Distant metastases, including intra-abdominal and intraperitoneal metastases, ± inguinal LNs
IIIB	Vaginal ± parametrial involvement		

FIGO: International Federation of Gynecology and Obstetrics

Treatment
- surgical: total hysterectomy + BSO
  - pelvic washings ± pelvic and para-aortic node dissection ± omentectomy in more advanced cases
  - goals: treatment, staging, determining need for adjuvant treatment
- adjuvant therapy: includes radiation and chemotherapy, depends on clinical and histological features
- hormone therapy: can be used in fertility-sparing treatments (e.g. progesterone IUD or oral progestins)

UTERINE SARCOMA
- rare; 3-9% of all uterine malignancies
- arise from stromal components (endometrial stroma, mesenchymal, or myometrial tissues)
- behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5 yr survival is 35%
- vaginal bleeding is the most common presenting symptom

Prognostic Factors
- FIGO stage (most important factor)
- Age
- Grade
- Histologic subtype
- Depth of myometrial invasion
- Presence of LVSI

Complications of Therapy

Surgical Complications
- Surgical site infection
- Lymphedema
- VTE
- Urinary retention
- UTI
- Pelvic lymphocyst
- Leg weakness
- Vaginal dryness

Radiation Complications
- Radiation fibrosis
- Cystitis
- Proctitis
- Long-term increase in other types of malignancy

Uterine Sarcoma – Presentation
Bleeding, abdominal distention, pelvic pressure

CA-125 is indicated for monitoring response to treatment

Table 23. Summary of Uterine Sarcoma Subtypes and Features

Type	Epidemiology	Features	Diagnosis	Treatment
PURE TYPE				
1. Leiomyosarcoma	Most common type of uterine sarcoma Average age of presentation is 55 yr, but may present in premenopausal patients Often coexists with benign leiomyomata (fibroids)	Histologic distinction from leiomyoma: 1. Increased mitotic count (>10 mitoses/10 high-power fields) 2. Tumour necrosis 3. Cellular atypia Rapidly enlarging fibroids in a premenopausal patient Enlarging fibroids in a postmenopausal patient	Often postoperatively after uterus removed for presumed fibroids Stage using FIGO 2009 staging for leiomyosarcomas and ESS	Hysterectomy ± BSO usually No routine pelvic lymphadenectomy Chemotherapy is used in cases of metastatic disease Radiation therapy does not improve local control or survival Poor outcomes overall, even for early-stage disease
2. Endometrial Stromal Sarcoma (ESS)	Usually presents in perimenopausal or postmenopausal patients with abnormal uterine bleeding	Abnormal uterine bleeding Good prognosis	Diagnosed by histology of endometrial biopsy or D&C Stage using FIGO 2009 staging for leiomyosarcomas and ESS	Hysterectomy & BSO (remove ovaries as ovarian hormones may stimulate growth) No routine pelvic lymphadenectomy Adjuvant therapy based on stage and histologic features (hormones and/or radiation) Hormonal therapy (progestins) may be used for metastatic disease
3. Undifferentiated Sarcoma	Rare; less common than leiomyosarcoma and ESS	Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack of smooth muscle or endometrial stromal differentiation Poor prognosis	Often found incidentally postoperatively for abnormal bleeding	Treatment primarily surgical Radiation and/or chemotherapy for advanced diseased or unresectable disease
MIXED TYPE				
4. Adenosarcoma	The rarest of the uterine sarcoma Mixed tumour of low malignancy potential	Present with abnormal vaginal bleeding Polypoid mass in uterine cavity	Mixture of benign epithelium with malignant low-grade sarcoma Often found incidentally at time of hysterectomy for PMB Stage using FIGO 2009 staging for adenosarcoma	Treatment is surgical with hysterectomy & BSO

Table 24. FIGO Staging of Uterine Sarcoma (2009)

Stage	Description	Stage	Description
I	**Tumour limited to uterus**	**III**	**Tumour invades abdominal tissues**
IA	<5 cm	IIIA	One site
IB	>5 cm	IIIB	More than one site
II	**Tumour extends beyond uterus**	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IIA	To the pelvis, adnexal involvement	**IV**	**Distant spread**
IIB	To extra-uterine pelvic tissue	IVA	Tumour invades bladder and/or rectum
		IVB	Distant metastasis

Ovaries are like GEMS
Germ cell
Epithelial
Metastatic
Sex cord stromal

Most (70%) epithelial ovarian cancers present at stage III disease

Ovary

BENIGN OVARIAN TUMOURS

- see *Table 25, GY45*
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour (rare)

Ovarian Tumour Markers
Epithelial cell:
- CA-125 (serous and endometrioid)

Sex-cord stromal cell:
- Granulosa cell: inhibin
- Sertoli-Leydig: androgens

Germ cell:
- Dysgerminoma: LDH
- Yolk sac: AFP
- Choriocarcinoma: β-hCG
- Immature teratoma: none
- Embryonal cell: AFP + β-hCG

MALIGNANT OVARIAN TUMOURS

- see *Table 25, GY45*

Diagnosis of ovarian tumours requires surgical pathology

Epidemiology

- lifetime risk 1.4%
- majority of ovarian cancer cases are detected in patients >50 yr
- causes more deaths in North America than all other gynecologic malignancies combined
- 4th leading cause of cancer death in women
- 85% epithelial; 15% non-epithelial
- 10-15% of epithelial ovarian cancers are related to hereditary predisposition

Any adnexal mass in postmenopausal women should be considered malignant until proven otherwise

Risk Factors (for epithelial ovarian cancers)

- early menarche and/or late menopause
- personal history of breast, colon, or endometrial cancer
- family history of breast, colon, endometrial, or ovarian cancer
- advanced age
- BRCA mutation (serous) and Lynch syndrome (non-serous, non-mucinous)
- use of fertility drugs (limited evidence)

Omental Cake: a term for ascites plus a fixed upper abdominal and pelvic mass; almost always signifies ovarian cancer

Protective Factors (for epithelial ovarian cancers)

- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use, 50% after 5 yr)
- pregnancy/breastfeeding

Prophylactic Measures

- prophylactic BSO in high-risk patients (i.e. BRCA mutation carriers)
- prophylactic salpingectomy in high-risk patients (i.e. BRCA mutation carriers who do not want oophorectomy yet)

Screening

- no effective method
- routine CA-125 or U/S not recommended

Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force
JAMA 2018;319(6):595-606
Purpose: To systematically review evidence on benefits and harms of ovarian cancer screening among average-risk, asymptomatic women.
Methods: Systematic review of RCTs of ovarian cancer screening in average-risk women that reported mortality or quality-of-life outcomes. Interventions included transvaginal U/S and/or CA-125 testing. Comparators were usual care or no screening.
Results: Four trials (n = 293587) were included. No trial found a significant difference in ovarian cancer mortality with screening. In two trials, screening led to surgery for suspected ovarian cancer in 1% of women without cancer and for transvaginal U/S with or without CA-125 screening in 3%, with major complications occurring in 3% to 15% of surgeries. Evidence of psychological harm was found in cases of repeat follow-up scans and tests.
Conclusions: Ovarian cancer mortality did not significantly differ between screened women and those with no screening or in usual care.

Clinical Features

- most patients with epithelial ovarian cancer present with advanced stage disease (i.e. stage IIIC high-grade serous histology)
- symptoms:
  - abdominal symptoms (nausea, bloating, pain, dyspepsia, anorexia, early satiety)
  - symptoms of mass effect
  - increased abdominal girth (from ascites or tumour itself)
  - urinary urgency and frequency
  - constipation

Treatment

- debulking surgery including total hysterectomy, BSO, omentectomy, and/or removal of all visible disease
- many epithelial ovarian cancers (i.e. serous ovarian carcinoma) are chemosensitive: treat with platinum-based chemotherapy + taxol
- neo-adjuvant chemotherapy (if needed) to shrink down tumours prior to debulking
- adjuvant chemotherapy to treat microscopic disease

Malignant Ovarian Tumour Prognosis

5 Yr Survival	
Stage I	75-95%
Stage II	60-75%
Stage III	23-41%
Stage IV	11%

Low Malignant Potential (also called "Borderline") Tumours

- a subcategory of epithelial ovarian cancer (~15% of all epithelial ovarian tumours)
- approximately one-third of tumours are identified in patients <40 yr
- pregnancy and breastfeeding are protective factors
- tumour cells with histologically malignant characteristics arise from the ovarian surface, but do not invade the ovarian stroma
- able to metastasize, but uncommon
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
  - chemotherapy has limited benefit: can be treated with hormonal manipulation (letrozole)
  - young patients can be treated with fertility-sparing options such as cystectomy or unilateral salpingo-oophorectomy
- generally slow growing, excellent prognosis
  - 5 yr survival >99%
  - recurrences tend to occur late, may be associated with low-grade serous carcinoma

Table 25. Ovarian Tumours

Type	Description	Presentation	Ultrasound/Cytology	Treatment
FUNCTIONAL TUMOURS (all benign)				
Follicular Cyst	Follicle fails to rupture during ovulation	Usually asymptomatic May rupture, bleed, tort, infarct, causing pain ± signs of peritoneal irritation	4-8 cm mass, unilocular, lined with granulosa cells	Symptomatic or suspicious masses warrant surgical exploration Otherwise if <6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle OCP (ovarian suppression): will prevent development of new cysts Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)
Corpus Luteum Cyst	Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic	More likely to cause pain than follicular cyst May delay onset of next period	Larger (10-15 cm) and firmer than follicular cysts	Same as for follicular cysts
Theca-Lutein Cyst	Due to atretic follicles, stimulated by abnormal β-hCG levels	Associated with molar pregnancy, ovulation induction with clomiphene		Conservative Cyst will regress as β-hCG levels fall
Endometrioma	See *Endometriosis, GY11*			
Polycystic Ovaries	See *Polycystic Ovarian Syndrome, GY25*			
BENIGN GERM CELL TUMOURS				
Benign Cystic Teratoma (dermoid)	Single most common ovarian germ cell neoplasm Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)	May rupture, twist, infarct 20% bilateral 20% occur outside of reproductive yr	Smooth-walled, mobile, unilocular U/S may show calcification which is pathognomonic	Treatment usually laparoscopic cystectomy; may recur
MALIGNANT GERM CELL TUMOURS				
General Information	Rapidly growing, 2-3% of all ovarian cancers	Usually children and young women (<30 yr)		Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy
Dysgerminoma	Produces LDH	10-15% bilateral		When diagnosed at stage IA, no adjuvant treatment is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
Immature Teratoma	No tumour marker identified	Almost always unilateral		When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated When diagnosed at Grade 2-3, either adjuvant chemotherapy or surgical staging is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
Yolk Sac Tumour	Produces AFP	Abdominal pain and pelvic mass		High grade tumour can be treated with adjuvant chemotherapy or monitor AFP levels
Ovarian Choriocarcinoma	Produces β-hCG	Precocious puberty and irregular vaginal bleeding		High grade tumour usually treated with adjuvant chemotherapy

Table 25. Ovarian Tumours

Type	Description	Presentation	Ultrasound/Cytology	Treatment
EPITHELIAL OVARIAN TUMOURS (malignant or borderline)				
General Information	Derived from mesothelial cells lining peritoneal cavity Classified based on histologic type 80-85% of all ovarian neoplasms (including malignant tumours)		Varies depending on subtype	**Borderline** Cystectomy vs. unilateral salpingo-oophorectomy **Malignant** 1. Early stage (stage I): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy). Depending on histology, may require adjuvant chemotherapy 2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatin/paclitaxel vs. intraperitoneal chemotherapy (stage III) neoadjuvant chemotherapy with IV carboplatin/paclitaxel, followed by delayed debulking with further adjuvant IV chemotherapy
Serous	Most common ovarian tumour histology 50% of all ovarian cancers 75% of epithelial tumours 70% benign	20-30% bilateral	Lining similar to fallopian tube epithelium Often multilocular Histologically contain psammoma bodies (calcified concentric concretions)	See above
Mucinous	20% of epithelial tumours	Rarely complicated by Pseudomyxoma peritonei: implants seed abdominal cavity and produce large quantities of mucin	Resembles endocervical epithelium Often multilocular May reach enormous size	Poor response to chemotherapy If mucinous, remove appendix as well to rule out possible source of primary disease
Clear Cell	10% of epithelial tumours Can be found adjacent to endometriosis More common in the Asian population	More likely to be detected at an early stage	Contains glycogen-rich cells with clear cytoplasm and hobnail cells	Poor response to chemotherapy
Endometrioid	10% of epithelial tumours Can be found adjacent to endometriosis	Can be associated with endometrial neoplasm	Typically cystic or solid, unilateral, and confined to the ovary	Tend to respond well to chemotherapy
SEX CORD STROMAL OVARIAN TUMOURS				
Fibroma/Thecoma (benign)	From mature fibroblasts in ovarian stroma	Non-functioning Occasionally associated with Meig's syndrome (triad of benign ovarian tumour, ascites, and pleural effusion)		
Granulosa-Theca Cell Tumours (benign or malignant)	Tumour marker is inhibin	Estrogen-producing: feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding) Risk of endometrial cancer due to estrogen	Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies	Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease
Sertoli-Leydig Cell Tumour (benign or malignant)	Can measure elevated androgens as tumour markers	Androgen-producing: virilizing effects (hirsutism, deep voice, recession of front hairline)		Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease
METASTATIC OVARIAN TUMOURS				
From GI Tract, Breast, Endometrium, Lymphoma	4-8% of ovarian malignancies Krukenberg tumour: metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast primary tumour)	80% bilateral	Krukenberg tumours have "signet-ring" cells	

Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
    - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for preoperative gynecologic oncology referral (see sidebar)
- physical exam findings largely dependent on stage of disease
- blood work: CBC, LFTs, electrolytes, Cr, tumour markers as appropriate (CA-125, inhibin, β-hCG, LDH, AFP, androgens, CEA, Ca19-9, estrogen)
- biopsy not recommended due to tumour spillage into peritoneum; if extensive disease, determine cytological diagnosis from paracentesis from ascites or tissue biopsy from peritoneal deposits or omental cake
- radiology
  - transvaginal U/S best to visualize ovaries
  - CT abdomen and pelvis to look for metastatic disease
  - bone scan or PET scan not indicated

Causes of Elevated CA-125

Age influences reliability of test as a tumour marker

50% sensitivity in early-stage ovarian cancer (poor), therefore not good for screening

Malignant

Gynecologic: ovary, uterus

Non-Gynecologic: pancreas, stomach, colon, rectum

Non-Malignant

Gynecologic: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID

Non-Gynecologic: cirrhosis, pancreatitis, renal failure

- try to rule out other primary source (if suspected), based on:
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms: gastroscopy ± upper GI series
  - abnormal vaginal bleeding: endometrial biopsy to rule out concurrent endometrial cancer; abnormal cervix: need to biopsy cervix (not Pap smear); breast lesion identified or risk factors present: mammogram

Table 26. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2014)

Stage	Description
I	Growth limited to the ovaries
IA	1 ovary, no ascites, no tumour on external surface, capsule intact, negative washings
IB	2 ovaries, no ascites, no tumour on external surface, capsule intact
IC	1 or 2 ovaries with any of the following: surgical spill (IC1), capsule ruptured (IC2), tumour on ovarian surface (IC2), or malignant cells in ascites (IC3)
II	**Growth involving one or both ovaries with pelvic extension or primary peritoneal cancer**
IIA	Extension ± implants to uterus/tubes
IIB	Extension to other pelvic structures
III	**Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal nodes**
IIIA	Positive retroperitoneal LNs and/or microscopic metastasis beyond pelvis
IIIA1	Positive retroperitoneal LNs
IIIA2	Microscopic, extrapelvic peritoneal involvement ± positive retroperitoneal LNs
IIIB	Macroscopic peritoneal metastasis beyond pelvis ≤2 cm, ± positive retroperitoneal LNs. Includes extension to capsule of liver/spleen
IIIC	Same as above but peritoneal metastasis >2 cm
IV	**Distant metastasis beyond peritoneal cavity**
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis or metastasis to extra-abdominal organs (inguinal LNs and LNs outside of abdominal cavity included)

FIGO = International Federation of Gynecology and Obstetrics

Cervix

MALIGNANT CERVICAL LESIONS

Epidemiology

- majority are SCC (90%); adenocarcinomas increasing (10%); rare subtypes include small cell, adenosquamous
- 8000 deaths annually in North America
- average age at presentation: 50 yr; bimodal distribution (increased frequency in 40s and 60s)

Etiology

- at birth, the vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from columnar to squamous)
  - a new squamocolumnar junction forms as a result
- the TZ is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (e.g. HPV) to get dysplasia
- dysplasia progresses to carcinoma *in situ* (CIS), which further progresses to invasion of cervical tissues
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

Risk Factors

- HPV infection
  - see *Sexually Transmitted Infections, GY28*
  - high-risk of neoplasia associated with types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82
  - low-risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high-risk HPV types
- high-risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high-risk male partner

A Risk of Malignancy Incorporating CA-125, Ultrasound, and Menopausal Status for the Accurate Preoperative Diagnosis of Ovarian Cancer
BJOG 1990;97:922-929
RMI = U x M x CA-125
Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

U = 1 (for U/S scores of 0 or 1)
U = 4 (for U/S scores of 2-5)
Menopausal Status
- Postmenopausal: M = 4
- Premenopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI>200: gynecologic oncology referral is recommended

Optimal Primary Surgical Treatment for Advanced Epithelial Ovarian Cancer
Cochrane Database Syst Rev 2011;(8):CD007565
Summary: During primary surgery for stage III or IV epithelial ovarian cancer, all attempts should be made to achieve complete cytoreduction. When this is not achievable, optimal (<1 cm) residual disease should be the goal.
Methods: Identified 11 retrospective studies consisting of 4735 women using comprehensive search strategy.
Results:
1. When suboptimal (margins >1 cm) was compared with optimal (<1 cm) cytoreduction, the survival estimates were reduced but remained statistically in favour of the lower volume disease group.
2. No significant difference in overall survival between suboptimal and optimal cytoreduction.
3. Borderline difference in progression-free survival when residual disease >2 cm and <2 cm were compared (p=0.05).

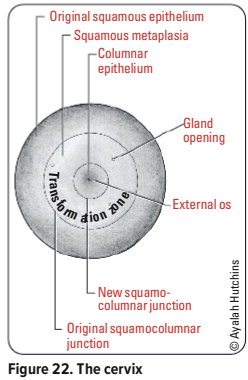


Figure 22. The cervix

Cervical cancer is most prevalent in developing countries and, therefore, is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies such as CT and MRI

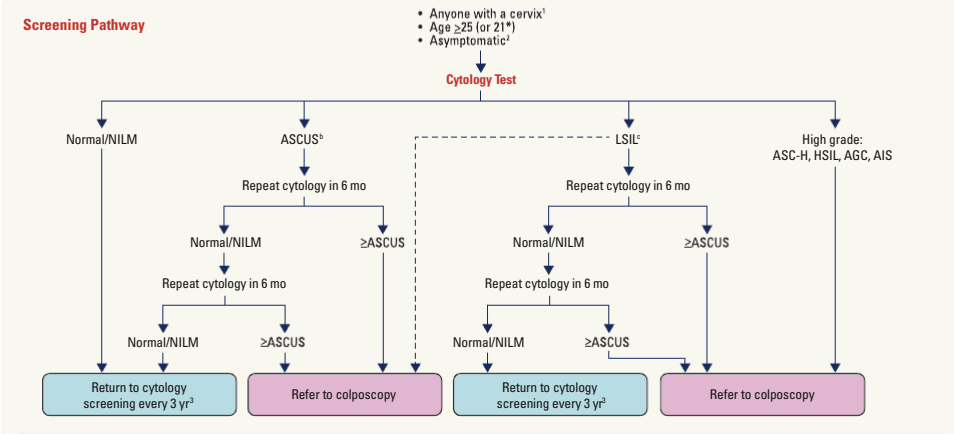
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include:
  - immigrant Canadians
  - Indigenous peoples in Canada
  - geographically-isolated Canadians
  - sex-trade workers
  - low socioeconomic status Canadians
  - immunocompromised individuals

Cervical Cancer Screening Guidelines (Pap Test)

- see Family Medicine, FM5

Clinical Features

- SCC: exophytic, fungating tumour
- adenocarcinoma: endophytic or exophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - postcoital bleeding
- late
  - 80-90% present with bleeding: either postcoital, postmenopausal, or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix



[1]These guidelines apply to anyone with a cervix including: women; pregnant people; transmen; non binary people; people who have undergone a subtotal hysterectomy; and people who have been vaccinated with the HPV vaccine
[2]Any visible cervical abnormalities or abnormal symptoms must be investigated. Consider referral to a specialist (e.g. colposcopist, gynaecologist, gynaeoncologist)
[3]Immunocompromised people may be at elevated risk and should receive annual screening
[a]Ontario Health (Cancer Care Ontario) is aware that the Screening Activity Report is not yet aligned with this guidance and will be updated with HPV implementation. Criteria for preventive care bonuses may not be updated during the interim period of changeover to HPV testing. Criteria for preventive care bonuses will be updated when HPV testing is implemented in screening
[b]HPV testing is not currently funded by the Ministry of Health. Primary care providers can consider HPV testing for those with ASCUS results on a patient pay basis or where available (i.e. in some hospital settings) for people ages 30 and older
[c]Repeat cytology or colposcopy are acceptable management options after the first LSIL result. Low grade abnormalities often regress on their own and may be best managed in surveillance, however colposcopy may be considered

Figure 23. Decision making chart for Pap test (not applicable for adolescents)

Adapted from: Ontario Cervical Screening Program. June 2020. Cervical screening guidelines unique to each province

Diagnosis

- colposcopy is a clinical procedure that facilitates identification and biopsy of suspicious cells
- in colposcopy:
  - apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
  - ECC if entire lesion is not visible or no lesion visible
  - diagnostic excision (LEEP) if:
    - unsatisfactory colposcopy (poor visualization/access to transformation zone)
    - discrepancy between cytology, colposcopy, and histological findings
    - positive findings/glandular abnormalities in endocervical curettage
    - suspicious for adenocarcinoma *in situ* (consider cold-knife conization)
    - recurrence of lesion post-ablation or excision
    - inability to rule out invasive disease, i.e. large lesions (lesions extending into endocervical canal, extending widely on cervix, or onto vaginal epithelium)
- consider cold-knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- any imaging modality or pathological findings are permitted for FIGO clinical staging

Table 27. FIGO Staging Classification of Cervical Cancer (Clinical Staging) (2018)

Stage	Description
I	**Confined to cervix**
IA	Diagnosed only by microscopy
IA1	Stromal invasion not >3 mm deep
IA2	3 mm to <5 mm deep
IB	Measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to cervix
IB1	Stromal invasion ≥5 mm deep and <2 cm wide
IB2	Stromal invasion ≥5 mm deep and ≥2 cm and <4 cm wide
IB3	≥4 cm in width
II	**Beyond uterus but not to the pelvic wall or lower 1/3 of vagina**
IIA	Limited to upper 2/3 of vagina, no obvious parametrial involvement
IIA1	Clinically visible lesion <4 cm wide
IIA2	Clinically visible lesion ≥4 cm wide
IIB	Obvious parametrial involvement, but not up to pelvic wall
III	**Extends to pelvic wall, and/or involves lower 1/3 of vagina, and/or causes hydronephrosis or non-functioning kidney, and/or involves pelvic and/or para-aortic lymph nodes**
IIIA	Involves lower 1/3 vagina but no extension into pelvic wall
IIIB	Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent
IIIC1	Pelvic lymph nodes metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	**Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (bullous edema does not permit a case to be allotted to stage IV)**
IVA	Spread of the growth to adjacent organs (bladder or rectum)
IVB	Distant metastases

Treatment: Prevention and Management

Prevention: HPV Vaccine

- two vaccines currently approved (Gardasil®, Cervarix®)

Table 28. Comparison of Two Vaccines against Human Papillomavirus (HPV)

	Gardasil®*	Cervarix®
Viral Strains Covered	6, 11, 16, 18, 31, 33, 45, 52, and 58	16, 18
Route of Administration	IM	IM
Schedule of Dosing	2 Dose: Second dose administered 6-12 mo after first dose 3 Dose: 0, 2, 6 mo	0, 1, 6 mo
Side Effects	Local: redness, pain, swelling General: headache, low grade fever, GI upset	Local: redness, pain, swelling General: headache, low grade fever, GI upset
Approved Age	Females ages 9-45, males ages 9-45	Females ages 9-45
Contraindications	Pregnancy and breastfeeding (limited data)	

*Gardasil-9 also covers types 31, 33, 45, 52, and 58; also used to prevent genital warts

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. LSIL, HSIL, or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy

Cervical Cancer Prognosis 5 yr Survival	
Stage 0	99%
Stage I	75%
Stage II	55%
Stage III	30%
Stage IV	7%
Overall	50-60%

Final Efficacy, Immunogenicity, and Safety Analyses of a Nine-Valent Human Papillomavirus Vaccine in Women Aged 16-26 Years: A Randomised, Double-Blind Trial
Lancet 2017;390:2143-2159
Purpose: A nine-valent HPV vaccine (9vHPV) was developed which covers additional strains of HPV compared to the quadrivalent vaccine (qHPV). This study reported the efficacy of the 9vHPV vaccine.
Methods: A randomized double-blind efficacy trial comparing the nine-valent HPV vaccine (9vHPV) to the quadrivalent HPV vaccine (qHPV) in 14215 women. The primary outcomes were incidence of high-grade cervical, vulvar, and vaginal diseases related to HPV-31, 33, 45, 52, and 58 and non-inferiority of anti-HPV 6, 11, 16, and 18 mean titres.
Results: The incidence of high-grade cervical, vulvar, and vaginal disease was 0.5 cases per 10000 person-yr for the 9vHPV group compared to 19 cases per 10000 person-yr for the qHPV group. HPV 6, 11, 16, and 18 titres were non-inferior in the 9vHPV group compared to the qHPV group. There were no clinically meaningful differences in severe adverse effects between groups.
Conclusions: The 9vHPV vaccine is effective at preventing infection, cytological abnormalities, and high-grade lesions and may offer broader protection against HPV and cervical cancer compared to the qHPV vaccine.

- should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
- may be given at the same time as hepatitis B or other vaccines using a different injection site
- not for treatment of active infections
- most patients will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease

Abnormal Pap Tests in Pregnancy

- incidence: 1 in 2200
- Pap test at initial prenatal visit if overdue for routine Pap test
  - if abnormal Pap or suspicious lesion, refer to colposcopy
  - if diagnostic conization required, should be deferred until T2 to minimize risk of pregnancy loss
  - if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
  - if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
    - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
    - recommendations in T2/T3: delay of therapy until viable fetus and C-section for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Table 29. Management of Abnormal Cervical Histology and Cervical Cancer

Histology Result from Colposcopy	Management
Normal	If histology results normal and cytology > LSIL, then repeat colposcopy in 6 mo
LSIL	**Women <25 yr** If cytology is LSIL, ASCUS, or normal, then annual Paps by primary care provider x 3 yr, followed by return to normal screening If cytology is HSIL, then consider pathology review, and/or reassessment every 6-12 mo in colposcopy **Women ≥ 25 yr** If HPV -: routine Pap screening every 3 yr If HPV +: follow-up colposcopy with cytology and HPV test (if 30 yr or older) in 1 yr
HSIL CIN II/CIN III	**Women ≥25 yr** Excisional procedures (e.g. cold knife, LEEP) or laser preferred Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage **Women <25 yr** Colposcopy every 6 mo for 2 yr or treatment may be acceptable based on patient preference
AIS	Repeat colposcopy + treatment (e.g. LEEP, cold-knife cone) ± endocervical curettage
Stage IA1 (no LVSI)	LEEP if future fertility desired (and lesion ≤2 cm) Simple hysterectomy if future fertility is not desired
Stage IA2, IB1, IB2	Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes or pelvic lymph node dissection) If high chance of adjuvant radiation then consider primary chemoradiation as more morbidity occurs from double-modality treatment (surgery and radiation) Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy Advantage is that ovaries can be spared if premenopausal, better sexual functioning For fertility preservation (if tumour <2 cm), may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease Chemoradiation therapy if adverse high-risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins or adverse cervical factors (2 or more): deep stromal invasion, size >4 cm, LVSI
Stages IB3 (>4 cm), II, III, IV	Primary chemoradiation therapy CT to assess extent of disease: evaluate pelvic and para-aortic nodes For positive nodes on PET: primary chemoradiation with extended field RT Hysterectomy generally not suggested following primary treatment with curative intent

Fallopian Tube

- least common site for carcinoma of the female reproductive system (0.3%)
- usually serous epithelial carcinoma
- new evidence shows that some serous ovarian cancers originate in the fallopian tube
- more common in fifth and sixth decade

Clinical Features

- classic triad present in minority of cases, but very specific
  - watery discharge (most specific): "hydrops tubae profluens"
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain

- most patients present with a pelvic mass (see *Pelvic Mass, GY42* and *Ovary, GY44* for guidelines regarding diagnosis/investigation)

Treatment
- same as for malignant epithelial ovarian tumours, see *Table 25, GY45*
- salpingectomy (removal of fallopian tubes to prevent ovarian cancer)

Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium
- biopsy is often necessary to make diagnosis and/or rule out malignancy:
  1. Lichen sclerosus
     - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
     - pruritus, dyspareunia, burning, bleeding, ulceration, excoriations
     - 'figure of 8' distribution
     - most common in postmenopausal patients but can occur at any age
     - patients should be monitored for malignancy, due to increased risk of SCC
     - treatment: high-potency topical steroid ointment (clobetasol), likely long-term treatment necessary
  2. Lichen simplex chronicus
     - surface of labia majora is thickened and hyperkeratotic, leather-like in appearance
     - most common symptoms: pruritus and burning, often at night
     - typically occurs in postmenopausal patients
     - treatment: medium-potency steroid ointment based on symptom severity + nighttime antihistamines
  3. Lichen planus
     - autoimmune disorder where T cells attack basal keratinocytes
     - peak incidence at age 30-60
     - 3 variants including erosive, papulosquamous, and hypertrophic
     - can extend into vaginal canal and cause loss of structure (desquamative vaginitis)
     - can have oral lichen planus in oral cavity
     - treatment: ultrapotent steroid ointment BID until plaques resolve, vaginal suppositories, or immunosuppressive therapies (e.g. cyclosporine) are all accepted

Any suspicious lesion of the vulva should be biopsied

Tumours
- papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNANT VULVAR LESIONS

Epidemiology
- 5% of genital tract malignancies
- 90% SCC; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
  - Type I disease: HPV-related (50-70%), usual or classical vulvar intraepithelial neoplasia (VIN)
    - more likely in younger patients
    - 90% of VIN contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy, differentiated VIN
    - usually postmenopausal patients
    - related to lichen sclerosis

Risk Factors
- HPV infection
- VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
- progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)
- history of cervical cancer
- cigarette smoking
- immunodeficiency
- vulvar lichen sclerosus

Clinical Features
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus, or white, red, or skin coloured papules, nodules, or plaques most common
- less common: ulcer, bleeding, discharge, pain, and dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal, then spreading to pelvic nodes)
  - hematogenous

Investigations
- ± vulvar biopsy
- always biopsy any suspicious lesion
  - do not remove entire lesion during biopsy (allows for site identification through sentinel LN injection if malignant)

Prognosis
- depends on stage: particularly nodal involvement (single most important predictor followed by tumour size)
  - lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

Treatment
- FIGO Stage I (tumour confined to vulva; no extension to adjacent perineal structures): radical local excision
- FIGO Stage II (tumour of any size with extension to adjacent perineal structures, no nodal metastases): modified radical vulvectomy
- FIGO stage III-IV (extension to any of: proximal 2/3 of urethra, proximal 2/3 of the vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or large/distant nodal metastases): sentinel lymph node biopsy followed by surgical resection of residual primary and adjuvant chemotherapy or radiation

Vagina

BENIGN VAGINAL LESIONS
- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

MALIGNANT VAGINAL LESIONS

Epidemiology
- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are SCC
- more than 50% diagnosed between 70-90 yr

Risk Factors
- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations
- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are metastatic from one of these sites)
- staging

Clinical Features

Table 30. Clinical Features of Malignant Vaginal Lesions

Type	Clinical Features
Vaginal Intra-Epithelial Neoplasia (VAIN)	Grades: analogous to cervical dysplasia
Squamous Cell Carcinoma (SCC)	Most common site is upper 1/3 of posterior wall of vagina Asymptomatic Painless vaginal discharge (often foul-smelling) and bleeding Vaginal bleeding especially during/post-coitus Urinary and/or rectal symptom 2° to compression
Adenocarcinoma	Most are metastatic, usually from cervix, endometrium, ovary, or colon Most primaries are clear-cell adenocarcinomas Two types: non-DES and DES syndrome

Treatment
- Stage I
  - radiation therapy: for tumours >2 cm diameter or tumour involvement of the middle or lower vagina
  - surgical excision: radical hysterectomy, upper vaginectomy, and bilateral pelvic lymphadenectomy
- Stage II-IV: primary radiation with or without chemotherapy

Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast
- GTD = abnormal, can be benign or lead to the malignant form, called GTN

Epidemiology
- 1/1000 pregnancies
- marked geographic variation (as high as 1/125 in Taiwan)
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

HYDATIDIFORM MOLE (GTD)

Complete Mole
- most common type of hydatidiform mole
- risk factors
  - geographic (most common in those of South East Asian background)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency not proven)
  - prior molar pregnancy

With development of HTN early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

Partial (or Incomplete) Mole
- associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations

Table 31. Features of Complete and Incomplete Hydatidiform Moles

	Complete	Incomplete
Pathology	Diffuse trophoblastic hyperplasia	Focal trophoblastic hyperplasia
Presence of Fetus	None	Associated with fetal tissue
Ultrasound Features	"Snowstorm" appearance due to swelling of villi	Degeneration of placenta Multiple echogenic regions Focal intrauterine hemorrhage
Genetics	Diploid Chromosomes completely of paternal origin	Triploid 1 set of maternal chromosomes 2 sets of paternal chromosomes
Clinical Presentation	Vaginal bleeding Uterine size large for dates Hyperemesis gravidarum Preeclampsia Hyperthyroid	Similar to spontaneous, threatened, missed abortion Vaginal bleeding
Risk of Progression of Malignancy	15-20%	<4%

Investigations
- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
- CXR (may show metastatic lesions)
- features of molar pregnancies at high-risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - β-hCG >100000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts >6 cm in diameter

Treatment
- for GTD: suction D&C (or rarely hysterectomy)
- Rhogam® if Rh-negative
- for GTN: single agent (i.e. methotrexate, actinomycin D) or multi-agent (i.e. EMACO, EMA-EP) chemotherapy based on WHO scoring system

Follow-up
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), and then one month after for incomplete hydatidiform mole or monthly for 6 mo if complete hydatidiform mole
- reliable contraception required to avoid pregnancy during entire follow-up period
- women who become pregnant during the follow-up period should be referred to gynecologic oncology and maternal-fetal medicine specialists
- increase or plateau of β-hCG indicates GTN: single or multi-agent chemotherapy based on WHO scoring system (see *Table 32*)

Table 32. WHO Prognostic Score for GTD (2011)

	Score			
Prognostic Factor	**0**	**1**	**2**	**4**
Maternal Age	<40	≥40		
Antecedent Pregnancy	Mole	Abortion	Term	
Interval (End of Antecedent Pregnancy to Chemotherapy in Months)	<4	4-6	7-13	>13
HCG IU/L	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Number of Metastases	0	1-4	5-8	>8
Site of Metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Largest Tumour Mass		3-5 cm	>5 cm	
Prior Chemotherapy			Single drug	Two drugs

A score of 6 or less is considered low-risk GTD. A score of 7 or more is considered high-risk GTD. A score of ≥ 13 is considered ultra high-risk GTD. The prognostic factor score is recorded after the FIGO score stage, separated by a colon

GTN (MALIGNANT GTD)

GTN Diagnosis
- β-hCG rise >10% compared with previous levels over 2 wk (e.g. 3 levels measured on days 1, 8, and 15) OR
- β-hCG plateau: <10% change/plateau compared with previous levels over 3 wk (e.g. 4 levels measured on days 1, 8, 15, and 22) OR
- histologic diagnosis of choriocarcinoma OR
- metastatic disease OR
- β-hCG level ≥20 000 mIU/mL >4 wk post-evacuation

Invasive Mole or Persistent GTN
- development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

Choriocarcinoma
- often presents with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, miscarriage, therapeutic abortion, ectopic pregnancy, or normal pregnancy

Placental-Site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

Classification of GTN
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% of patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma, which tends toward early vascular invasion and widespread dissemination

- if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
  - lungs (80%): cough, hemoptysis, CXR lesion(s)
  - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
  - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
  - liver (10%): elevated LFTs, U/S, or CT findings
  - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
- highly vascular tumour, which is more likely to bleed and result in anemia
- all have rising or plateau of β-hCG
- classification of metastatic GTN
  - divided into good prognosis and bad prognosis
  - features of bad prognosis
    - long duration (>4 mo from antecedent pregnancy)
    - high pre-treatment β-hCG titre: >100000 IU/24 h urine or >40000 IU/L of blood
    - brain or liver metastases
    - prior chemotherapy
    - metastatic disease following term pregnancy
  - good prognosis characterized by the absence of each of these features

Investigations (for Staging)

- blood work: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis only
- if CXR shows lung metastasis then CT abdomen/pelvis, MRI brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG
- ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases

Lungs are the primary site for malignant GTN metastases; when pelvic exam and CXR are negative, metastases are uncommon

Table 33. FIGO Staging and Management of Malignant GTN

Stage	Findings	Management
I	Disease confined to uterine corpus	Single agent chemotherapy for low-risk disease (WHO score ≤6) 1st line: pulsed actinomycin D (Act-D) IV q2 wk Alternatives: methotrexate (MTX)-based regimen 20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high-risk (WHO score ≥7) or if resistant to single-agent chemotherapy Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour
II	Metastatic disease to genital structures	As above
III	Metastatic disease to lungs with or without genital tract involvement	As above
IV	Distant metastatic sites including brain, liver, kidney, GI tract	Ultra high-risk patients should have low-dose induction chemotherapy weekly for 1-3 wk, followed by multi-agent chemotherapy

Follow-up (for GTN)

- contraception for all stages to avoid pregnancy during entire follow-up period, recommended combined OCP
- stage I, II, III
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 6-12 mo
- stage IV
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 24 mo

Common Medications

Table 34. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
acyclovir (Zovirax®)	Antiviral; inhibits DNA synthesis and viral replication	**First Episode**: 400 mg PO TID x 7-10 d **Recurrence**: 400 mg PO TID x 5 d	Genital herpes	**S/E**: headache, GI upset **D/I**: zidovudine, probenecid
bromocriptine (Parlodel®)	Dopaminomimetic, agonist at D2 Receptor and antagonist at D1 Receptor; acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin	**Initial**: 1.25-2.5 mg PO once daily at night with food **Then**: increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response **Usual Range**: 1.5-15 mg once daily For IVF: **Initial**: 1.25 mg/d PO between days 4-6 of follicular phase **Then**: 2.5 mg/d until 3 d after onset menstruation	Galactorrhea + amenorrhea 2° to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas) IVF	**S/E**: N/V, headache, postural hypotension, somnolence **C/I**: uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding **D/I**: domperidone, macrolides, octreotide
clomiphene citrate (Clomid®)	Increases output of pituitary gonadotropins to induce ovulation	50 mg once daily x 5 d Try 100 mg or 160 mg once daily If ineffective 3 courses: adequate trial	Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy	**S/E**: Common: hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare: ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects **C/I**: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding
clotrimazole (Canesten®)	Antifungal; disrupts fungal cell membrane	**Tablet**: 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose **Cream** (1 or 2%): 1 applicator intravaginally QHS x 3-7 d **Topical**: apply BID x 7 d	Vulvovaginal candidiasis	**S/E**: vulvar/vaginal burning
combined oral contraceptive pill (OCP)	Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration		Contraception Disorders of menstruation	See Tables 7-10, *GY15* and Table 12, *GY19*
dienogest (Visanne®)	Synthetic progestin	2 mg PO	Pelvic pain associated with endometriosis	**S/E**: changes to menstrual pattern, VTE **C/I**: pregnancy, lactation, liver disease/ malignancy, VTE disorders, cardiovascular disease, hormone-dependent tumours, undiagnosed AUB
doxycycline	Tetracycline derivative; inhibit protein synthesis	100 mg PO BID x ≥7 d	Chlamydia, gonococcal infection, syphilis	**S/E**: GI upset, hepatotoxicity **C/I**: pregnancy, severe hepatic dysfunction **D/I**: warfarin, digoxin
elagolix (Orlissa®)	Synthetic GnRH antagonist; induces reversible hypoestrogenic state	150 mg PO daily or 400 mg PO BID	Endometriosis, emerging evidence for fibroids, adenomyosis	**S/E**: hot flushing, nausea, headache **C/I**: pregnancy, osteoporosis, undiagnosed vaginal bleeding, severe hepatic dysfunction **D/I**: Organic Anion Transport Protein (OATP) 1B1 inhibitors
fluconazole (Diflucan®)	Antifungal; disrupt fungal cell membrane	150 mg PO x 1 dose	Vulvovaginal candidiasis unresponsive to clotrimazole	**S/E**: headache, rash, N/V, abdominal pain, diarrhea **D/I**: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin
intrauterine device (IUD) **copper IUD (Nova-T®)** **progesterone-releasing IUD (Mirena®, Kyleena®)**	Copper IUD: mild foreign body reaction in endometrium, which is toxic to sperm and alters sperm motility Progesterone-releasing IUD: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last 3 yr; up to 5 yr (Copper IUD, Mirena®, Kyleena®)	Contraception Disorders of menstruation	See Tables 7-10, *GY15* and Table 12, *GY19*
leuprolide (Lupron®)	Synthetic GnRH antagonist; induces reversible hypoestrogenic state	3.75 mg IM q1 mo or 11.25 mg IM q3 mo Usually ≤6 mo, check bone density if >6 mo Retreatment with Lupron® alone not recommended because of effects on bone density	Endometriosis Leiomyomata DUB Precocious puberty	**S/E**: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset **C/I**: pregnancy, undiagnosed vaginal bleeding, breastfeeding

Table 34. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
menotropin (Pergonal®)	Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development	75-150 IU of FSH and LH IM once daily x 7-12 d, then 10000 IU HCG 1 d after last dose	Infertility	**S/E**: bloating, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy **C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding
metronidazole (Flagyl®)	Bactericidal; forms toxic metabolites which damage bacterial DNA	2 g PO x 1 dose or 500 mg PO BID x 7 d	Bacterial vaginosis, trichomonas vaginitis	**S/E**: headache, dizziness, N/V, diarrhea, disulfiram-like reaction (flushing, tachycardia, N/V) **C/I**: pregnancy (1st trimester) **D/I**: cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine
nexplanon (etonogestrel implant)	Releases progestin which causes decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last up to 3 yr	Contraception Disorders of menstruation	See Tables 7-10, *GY15* and Table 12, *GY19*
oxybutynin (Ditropan®)	Anticholinergic; relaxes bladder smooth muscle, inhibits involuntary detrusor contraction	5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d	Overactive bladder (urge incontinence)	**S/E**: dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache **C/I**: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function
tolterodine (Detrol®)	Anticholinergic	1-2 mg PO BID	Overactive bladder (urge incontinence)	**S/E**: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain **C/I**: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function
tranexamic acid (Cyklokapron®)	Anti-fibrinolytic; reversibly inhibits plasminogen activation	1-1.5 g TID-QID for first 4 d of cycle Max 4 g/d Ophthalmic check if used for several wk	Menorrhagia	**S/E**: N/V, diarrhea, dizziness, rare cases of thrombosis, abdominal pain, MSK pain **C/I**: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age <15 yr
ulipristal acetate (Fibristal®) -withdrawn from market in 2020 urofollitropin (Metrodin®)	Selective progesterone receptor modulator (SPRM)	5 mg PO once daily for max 3 mo; first tablet taken anytime during first 7 d of menstruation	Leiomyoma (preoperative)	**S/E**: headache, hot flushes, constipation, vertigo, endometrial thickening **C/I**: pregnancy, undiagnosed vaginal bleeding, any gynecological cancer
urofollitropin (Metrodin®)	FSH	75 IU/d SC x 7-12 d	Ovulation induction in PCOS	**S/E**: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy **C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding

Landmark Gynecology Trials

Trial Name	Reference	Clinical Trial Details
Endometrial Cancer		
PORTEC-3	LANCET 2019; 20(9):1273-1285	**Title**: Adjuvant Chemoradiotherapy versus Radiotherapy Alone in Women with High-Risk Endometrial Cancer (PORTEC-3): Patterns of Recurrence and Post-Hoc Survival Analysis of a Randomised Phase 3 Trial **Purpose**: To investigate the benefit of combined adjuvant chemotherapy and radiotherapy vs. pelvic radiotherapy alone for women with high-risk endometrial cancer. **Methods**: Women with high-risk endometrial cancer were randomly assigned to receive radiotherapy alone or chemoradiotherapy. The co-primary endpoints were overall survival and failure-free survival. Secondary endpoints included vaginal, pelvic, and distance recurrence. **Results**: At a median of 72.6 mo, 5 yr overall survival was 81.4% with chemoradiotherapy vs. 76.1% with radiotherapy, and 5 yr failure-free survival was 76.5% with chemoradiotherapy vs. 69.1% with radiotherapy. Distant metastases occurred in 78/330 women in the chemoradiotherapy group vs. 98/330 in the radiotherapy group. **Conclusions**: For women with stage 3 or serous endometrial cancers, or both, chemoradiotherapy should be recommended over radiotherapy alone.
Cervical Cancer		
LACC	NEJM 2018; 379:1895-1904	**Title**: Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer **Purpose**: To investigate survival outcomes after laparoscopic or robot-assisted radical hysterectomy (minimally invasive surgery) vs. open abdominal radical hysterectomy (open surgery). **Methods**: Patients with stage A1, IA2, or IB1 cervical cancer and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, were randomly assigned to undergo minimally invasive surgery or open surgery. **Results**: The rate of disease-free survival at 4.5 yr was 86% with minimally invasive surgery and 96.5% with open surgery, a difference of -10.6% (95% confidence interval [CI], −16.4 to −4.7). Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3 yr rate, 91.2% vs. 97.1%) and a lower rate of overall survival (3 yr rate, 93.8% vs. 99.0%). **Conclusions**: Among women with early-stage cervical cancer, minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy.
Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix	J Clin Oncology 2000; 18(8):1606-1613	**Title**: Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix **Purpose**: Determine whether adjuvant cisplatin-based chemotherapy (CT) in addition to pelvic radiation therapy (RT) has benefit for early stage, high risk cervical cancer. **Methods**: In this multi-center trial, patients with stage IA2, IB, and IIA cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy, with high-risk prognostic factors on surgical sample were randomized to CT+RT (n=127) and RT (n=116). Primary outcomes were progression free and overall survival. **Results**: 4-year progression free survival was 80% in the CT-RT group and 63% in the CT group. CT-RT improved both progression-free survival (HR, 2.01; p = 0.003) and overall survival (HR, 1.96; p = 0.007). **Conclusions**: CT+RT adjuvant therapy following radical surgery improved survival for high-risk, early-stage cervical cancer.
Ovarian Cancer		
LION	NEJM 2019; 380:822-832	**Title**: A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms **Purpose**: Clarify role for pelvic and para-aortic lymphadenectomy in surgical treatment of patients with advanced ovarian cancer. **Methods**: In this international, multi-center trial, patients with advanced epithelial ovarian cancer who underwent macroscopically complete resection and had negative lymph nodes before and during surgery, were randomized to lymphadenectomy (n=323) or no lymphadenectomy (n=324). The primary outcome was overall survival. **Results**: Median overall survival was 65.5 mo in the lymphadenectomy and 69.2 mo in the no lymphadenectomy (HR, 1.06; 95% CI, 0.83-1.34; p = 0.65). Incidence of repeat laparotomy was higher in the lymphadenectomy at 12.4% compared to 6.5% in the no lymphadenectomy group (p = 0.01). **Conclusions**: Pelvic and para-aortic lymphadenectomy in surgically treated advanced ovarian cancer was not associated with longer overall survival and increased risk of complications.

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H Hematology

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Acronyms

Ab	antibody
AFib	atrial fibrillation
AFLP	acute fatty liver of pregnancy
aHUS	atypical hemolytic uremic syndrome
AIHA	autoimmune hemolytic anemia
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APC	activated protein C
APL	acute promyelocytic leukemia
APLA	antiphospholipid antibodies
APS	antiphospholipid antibody syndrome
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ATIII	antithrombin III
ATRA	all-trans retinoic acid
BM	bone marrow
CALR	calreticulin
CAR	chimeric antigen receptor
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CRP	C-reactive protein
DAT	direct antiglobulin test
DDAVP®	desmopressin
DIC	disseminated intravascular coagulation
DLBCL	diffuse large B-cell lymphoma
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EDTA	ethylenediaminetetraacetic acid
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESR	erythrocyte sedimentation rate
ET	essential thrombocythemia
FDP	fibrin degradation products
FNA	fine needle aspiration
FP	frozen plasma
G-CSF	granulocyte-colony stimulating factor
GSH	reduced glutathione
GU	genitourinary
GVHD	graft versus host disease
HA	hemolytic anemia
Hb	hemoglobin
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIT	heparin-induced thrombocytopenia
HL	Hodgkin lymphoma
HMWK	high molecular weight kininogen
HUS	hemolytic uremic syndrome
IBD	inflammatory bowel disease
IMF	idiopathic myelofibrosis
IMID	immunomodulatory drugs
INR	international normalized ratio
IPC	intermittent pneumatic compression
IPSS	international prognostic scoring system
ITP	immune thrombocytopenia
JAK2	Janus kinase 2
LAD	lymphadenopathy
LMWH	low molecular weight heparin
MAHA/TMA	microangiopathic hemolytic anemia/thrombotic microangiopathy
MCH	mean corpuscular Hb
MCHC	mean corpuscular Hb concentration
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MF	myelofibrosis
MGUS	monoclonal gammopathy of unknown significance
MM	multiple myeloma
MPN	myeloproliferative neoplasm
MPV	mean platelet volume
MUGA	multi-gated acquisition
NHL	non-Hodgkin lymphoma
OCP	oral contraceptive pill
PCC	prothrombin complex concentrates
PE	pulmonary embolism
PFS	progression-free survival
Ph	Philadelphia chromosome
PI	proteasome inhibitors
PK	prekallikrein
PMN	polymorphonuclear neutrophil
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PTT	partial thromboplastin time
PUD	peptic ulcer disease
PV	polycythemia vera
RCMD	refractory cytopenia with multilineage dysplasia
RCMD-RS	refractory cytopenia with multilineage dysplasia and ringed sideroblasts
RDW	RBC distribution width
SCD	sickle cell disease
SCT	stem cell transplantation
SPEP	serum protein electrophoresis
sTfR	soluble transferrin receptor
TCL	T-cell lymphoma
TIBC	total iron binding capacity
TKI	tyrosine kinase inhibitor
T-LGL	T-cell large granular lymphocyte
TLS	tumour lysis syndrome
tPA	tissue plasminogen activator
TPO	thrombopoietin
TT	thrombin time
TTP	thrombotic thrombocytopenic purpura
UFH	unfractionated heparin
UPEP	urine protein electrophoresis
VTE	venous thromboembolism
VWD	von Willebrand disease
VWF	von Willebrand factor
WHO	World Health Organization
XRT	radiation therapy

Basics of Hematology

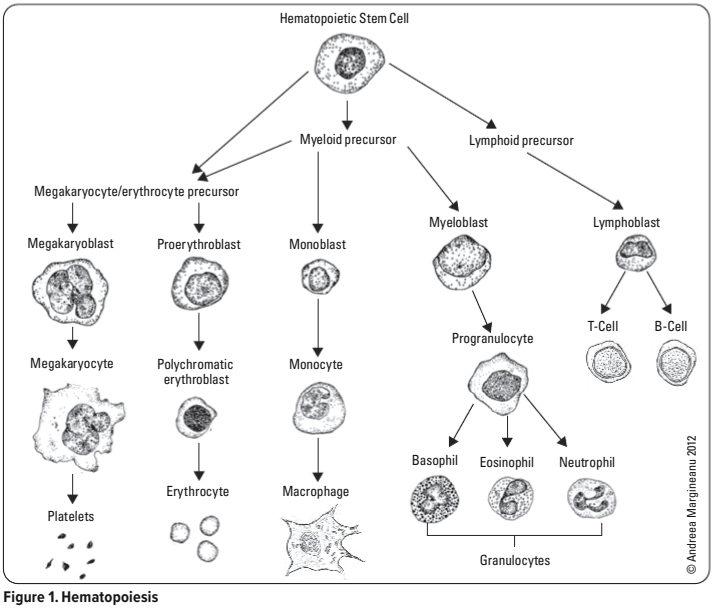

Figure 1. Hematopoiesis

Erythrocyte: carries oxygen from lungs to peripheral tissues
Reticulocyte: immature erythrocyte
Hb: protein contained in erythrocytes which binds oxygen
Neutrophil: granulocyte integral in innate immunity; main cell in acute inflammation
Eosinophil: granulocyte involved in response to parasites (especially helminths) and allergic response
Basophil: granulocyte mainly involved in allergy and parasitic infection
Lymphocyte: integral cell in adaptive immunity
Monocyte: involved in innate immunity; can differentiate into macrophage or dendritic cell
Platelet: mediator of primary hemostasis
Plasma: acellular, fluid component of blood containing water and proteins (including coagulation factors and immunoglobulins)
Serum: equivalent to plasma minus coagulation factors

- over 10 [11]blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies, and cranium
- lifespan of mature cells in blood
  - erythrocytes (90-120 d), neutrophils (~1 d), platelets (7-10 d), lymphocytes (varies – memory cells persist for years)

- role of lymphoid organs
  - spleen - part of reticuloendothelial system: sequesters aged RBCs, removes opsonized cells, and site of Ab production
  - thymus - involutes with age: site of T-cell maturation
  - lymph nodes: sites of B- and T-cell activation (adaptive immune response)

Complete Blood Count

Table 1. Common Terms Found in the CBC

Test	Definition	Normal Values*
RBC Count	Number of RBCs per volume of blood	3.5-5.0 x 10^{12}/L (female) 4.0-5.5 x 10^{12}/L (male)
Hb	Amount of Hb in the blood	115-155 g/L (female) 125-170 g/L (male)
Hct	Percentage of a given volume of whole blood occupied by packed RBCs	38-50%
MCV	Average RBC size	80-100 fL
MCH	Average amount of Hb per RBCs	25-34 pg (female) 27-34 pg (male)
MCHC	Average concentration of Hb inside RBCs	315-355 g/L
RDW	Percentage of variance in RBC size	11.5-15.5%
Reticulocyte Count	Number of reticulocytes per volume of blood	23-90 x 10^9/L (0.5-1.5%)
ESR	Rate at which RBCs separate from the serum, becoming sediment in the bottom of the test tube	<20 mm/h (female) <10 mm/h (male)
WBC Count	Number of WBCs per volume of blood	3.5-10.5 x 10^9/L
WBC Differential	Segmented neutrophils Band neutrophils Basophils Eosinophils Lymphocytes Monocytes	2-7 x 10v/L <0.7 x 10^9 /L <0.10 x 10^9/L <0.5 x 10^9/L 0.8-3.3 x 10^9/L (female) 0.8-3.5 x 10^9/L (male)L 0.1-1.0 x 10^9/L
Platelet Count	Number of platelets per volume of blood	130-380 x 10^9/L
Mean Platelet Volume (MPV)	Measurement of platelet size	9.0-14.0 fL

*All values apply to adults. Reference standards do not apply to all ethnic groups.

To estimate Hb based on the Hct, multiply by 3

Approach to Interpreting a CBC

1. consider values in the context of an individual's baseline:
   - up to 5% of population without disease may have values outside "normal" range
   - an individual may display a clinically significant change from their baseline without violating "normal" reference range
2. is one cell line affected or are several?
   - if all lines are low: pancytopenia (see *Pancytopenia, H8*)
   - if RBCs and platelets are low: consider a MAHA/TMA (see *Microangiopathic Hemolytic Anemia/ Thrombotic Microangiopathy, H23*) or an autoimmune process (Evan's Syndrome)
   - if single cell line affected: see *Common Presenting Problems, H6*

Clinical Use of RDW
To distinguish the etiologies of microcytosis:
Iron deficiency: increased RDW (anisocytosis) as cells are of varying sizes in iron deficiency
β-thalassemia minor: normal RDW (also expect a high RBC count) as cells are of similar size because the red cell abnormality is not progressive

Blood Film Interpretation

RED BLOOD CELLS

Size

- microcytic (MCV <80 fL), normocytic (MCV = 80-100 fL), macrocytic (MCV >100 fL)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, HAs, MF, blood transfusion, and MDS

Colour

- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
  - iron deficiency anemia, anemia of chronic disease, and sideroblastic anemia
- polychromasia: suggests increased reticulocytes (pinkish-blue cells)
  - increased RBC production by BM

Shape

- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, hemoglobinopathies, MF, severe B_{12} deficiency, MDS, and burns

Table 2. Common Erythrocyte Shapes

Shape	Definition	Associated Conditions
Discocyte	Biconcave disc	Normal RBC
Spherocyte	Spheroidal RBC (due to membrane defect or loss of membrane) Loss of central pallor	Hereditary spherocytosis, immune hemolytic anemia
Elliptocyte/Ovalocyte	Oval-shaped, elongated RBCs • Elliptocytes: the RBC long axis is ≥2x the length of the short axis • Ovalocytes: the RBC long axis is <2x the length of the short axis	Hereditary elliptocytosis, megaloblastic anemia, MF, iron-deficiency anemia (pencil forms), and MDS
Schistocyte (helmet cell, fragment)	Fragmented cells (due to traumatic disruption of membrane)	MAHA/TMA (HUS, aHUS, TTP, DIC, preeclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, burns, and prosthetic heart valves
Sickle Cell	Sickle-shaped RBC (due to polymerization of HbS)	Sickle cell disorders: HbSC, HbSS
Codocyte (target cell)	"Bull's eye" (due to a surface that is disproportionately large compared to their volume)	Liver disease, HbSC, thalassemia, iron deficiency anemia, and asplenia
Dacrocyte (teardrop cell)	Single pointed end, looks like a teardrop	MF, MDS, β-thalassemia, megaloblastic anemia, and BM infiltration
Acanthocyte (spur cell)	Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipid or protein composition)	Severe liver disease (spur cell anemia), starvation/anorexia, and post-splenectomy
Echinocyte (burr cell)	RBC with numerous regularly spaced, small, spiny projections	Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, and storage artifact
Rouleaux Formation	Aggregates of RBCs resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)	Pregnancy is most common cause (due to physiological increase in fibrinogen), inflammatory conditions (due to polyclonal immunoglobulins), plasma cell dyscrasias (due to monoclonal paraproteinemia, e.g. MM, macroglobulinemia), and storage artifact

Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

Table 3. RBC Inclusions

Inclusions	Definition	Associated Conditions
Nucleus	Present in erythroblasts (immature RBCs)	Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, and MPNs (MF)
Heinz Bodies	Denatured and precipitated Hb	G6PD deficiency (post-exposure to oxidant), thalassemia, and unstable Hb
Howell-Jolly Bodies	Small spherical nuclear remnant, typically in periphery and ordinarily removed by the spleen	Post-splenectomy, hyposplenism (SCD), neonates, and megaloblastic anemia
Basophilic Stippling	Deep blue granulations indicating ribosome aggregation	Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, MDS, and hereditary (pyrimidine 5'-nucleotidase deficiency)
Sideroblasts	Late erythrocytes in BM with Fe-containing granules in the cytoplasm	Hereditary, idiopathic, drugs, ethanol, hypothyroidism (see *Sideroblastic Anemia, H17*), MDS, and toxins (Pb)

Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

WHITE BLOOD CELLS

lymphocytes
- comprise 30-40% of WBCs; great variation in "normal" lymphocyte morphology
- the major classes of lymphocytes include: T cells, B cells, and natural killer (NK) cells
- nucleus occupies ~90% of cytoplasm

- neutrophils
  - normally, only mature neutrophils (with 3-4 lobed nuclei) and band neutrophils (immediate precursor with horseshoe-shaped nuclei) are found in circulation
  - hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B_{12} or folate deficiency)
  - left shift (increased granulocyte precursors)
    - seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, MPNs (CML, MF), and G-CSF (growth factor that stimulates neutrophil production) use
- blasts
  - immature, undifferentiated precursors; associated with acute leukemia, MDS, and G-CSF use

Table 4. Abnormal WBC on Film

Appearance	Definition	Associated Conditions
Smudge Cell	Lymphocytes damaged during blood film preparation indicating cell fragility	CLL and other lymphoproliferative disorders
Auer Rod	Cytoplasmic inclusions that form long needles in the cytoplasm of myeloblasts	Pathognomonic for AML
Atypical Lymphocyte	Pale blue cytoplasm with pink granules. Cytoplasm is indented by RBC edges	Viruses (particularly EBV) and T-LGL leukemia

Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012 and Danielle Sayeau 2017

Left Shift

Refers to an increase in granulocyte precursors in the peripheral blood film (myelocytes, metamyelocytes, promyelocytes, blasts). If present, implies increased marrow production of granulocytes (e.g. inflammation, infection, G-CSF administration, CML)

The presence of predominantly blasts in the peripheral smear without further differentiated precursor cells or mature neutrophils, suggests clonal cell disorder (MDS, acute leukemias)

If >20% of the total WBC differential consists of blasts, this is acute leukemia and is a medical emergency

PLATELETS

- small, purple, anuclear cell fragments

Bone Marrow Aspiration and Biopsy

- sites: posterior iliac crest/spine, sternum (aspiration only)
- analyses: most often done together
  - aspiration: takes a fluid marrow sample for cellular morphology (includes iron stain), flow cytometry, cytogenetics, molecular studies, and microbiology (C&S, acid-fast bacilli smear and culture, and PCR)
    - note: differential diagnosis for a "dry tap": MF, hairy cell leukemia, BM infiltration
  - biopsy: takes a sample of intact BM to assess histology (architecture) and immunohistochemistry
  - only aspirates, not biopsies, can be obtained from the sternal site

Indications

- unexplained CBC abnormalities
- diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, and solid tumours
- diagnosis and staging of lymphoma or solid tumours
- evaluate iron metabolism and stores (gold standard, but rarely done)
- evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher's disease)
- evaluate fever of unknown origin, suspected mycobacterial, fungal, and parasitic infections, or granulomatous disease
- evaluate unexplained splenomegaly
- confirm normal BM in potential allogeneic hematopoietic cell donor

Important Considerations

- do not perform a BM biopsy if there is evidence of infection over the targeted skin site
- risk of procedure: 1/100 chance of bleeding, very rare infection risk

Common Presenting Problems

Anemia

Definition

- a decrease in RBC mass that can be detected by Hb concentration, Hct, and RBC count
  - adult males: Hb <130 g/L or Hct <38%
  - adult females: Hb <120 g/L or Hct <37% (changes with pregnancy and trimester)

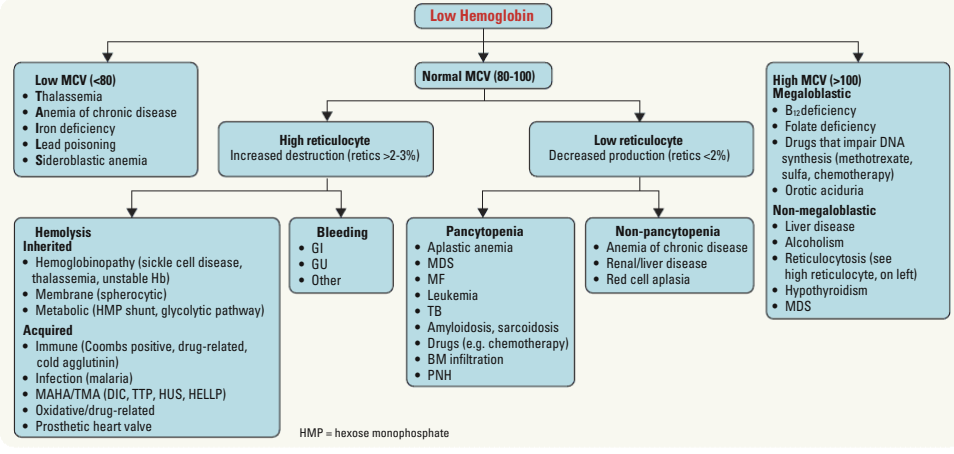

Figure 2. Approach to anemia – classification by MCV

Clinical Features

- history
  - symptoms of anemia: fatigue, headache, light-headedness, malaise, weakness, decreased exercise tolerance, dyspnea, palpitations, dizziness, tinnitus, and syncope
  - acute vs. chronic, bleeding, systemic illness, travel, medications, diet (Fe, B_{12} sources), alcohol, and family history
  - symptoms of hemolysis: jaundice, icterus
  - menstrual history: menorrhagia, menometrorrhagia
  - rule out pancytopenia (recurrent infection, mucosal bleeding, and easy bruising)
- physical signs
  - HEENT: pallor in mucous membranes and conjunctiva at Hb <90 g/L, ocular bruits at Hb <55 g/L, angular cheilitis, and jaundice
  - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, and signs of CHF
  - dermatologic: ecchymosis, petechiae, pallor in palmar skin creases at Hb <75 g/L, jaundice (if due to hemolysis), nail changes (spooning), and glossitis
  - splenomegaly, lymphadenopathy

Reticulocytes

- Reticulocytes are immature erythrocytes and are markers of erythrocyte production (↑ colour, ↓ central pallor, ↑ size)
- The reticulocyte count should always be interpreted in the context of Hb concentration
- The reticulocyte count should normally increase in response to a decrease in RBC
- With blood loss, reticulocytes should increase 2-3x initially and then 5-7x over the next week
- A normal reticulocyte count in anemia should be interpreted as a sign of decreased production, and may result from BM infiltration, nutritional deficiency, or other causes
- Anemia with reticulocytosis suggests appropriate BM response

Investigations

- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential, reticulocyte count, and blood film
- rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
- additional laboratory investigations as indicated (see *Microcytic Anemia, H14, Normocytic Anemia, H17, Hemolytic Anemia, H18,* and *Macrocytic Anemia, H25*)
- N.B. may have a mixed picture with multiple concomitant nutritional deficiencies

Treatment

- treat underlying cause (see *Microcytic Anemia, H14, Normocytic Anemia, H17, Hemolytic Anemia, H18,* and *Macrocytic Anemia, H25*)

Erythrocytosis

Definition

- an increase in Hb and/or Hct: Hb >165 g/L or Hct >49% (males); Hb >160 g/L or Hct >48% (females)

Etiology

- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, and "stress" (Gaisböck's syndrome)
- absolute erythrocytosis

Table 5. Etiology of Erythrocytosis

Primary	Secondary	Inappropriate Production of Erythropoietin
PV (see *Polycythemia Vera, H43*)	Physiologic (poor tissue oxygenation/hypoxia)	Tumours
	Carbon monoxide poisoning	Hepatocellular carcinoma
	Heavy smoking	Renal cell carcinoma
	High altitude	Cerebellar hemangioblastoma
	Pulmonary Disease	Pheochromocytoma
	COPD	Uterine leiomyoma
	Sleep apnea	Ovarian tumour
	Pulmonary hypertension	Other
	Cardiovascular Disease	Polycystic kidney disease
	R to L shunt (Eisenmenger syndrome)	Renal artery stenosis
	Hemoglobinopathy	Post-kidney transplant
	High O2 affinity Hb	Hydronephrosis
	Methemoglobinemia	Androgens
		Exogenous EPO
		SGLT2 inhibitors

Clinical Features

- secondary to high red cell mass and hyperviscosity
  - headache, dyspnea, dizziness, tinnitus, visual disturbances, hypertensive symptoms, and paresthesia
  - symptoms of angina, CHF, and aquagenic pruritus (only in MPNs)
- thrombosis (venous or arterial) or bleeding (seen with acquired VWD or acquired platelet dysfunction in MPNs)
- physical findings
  - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

Investigations

- serum EPO: differentiates primary (low/normal) from other etiologies (elevated)
  - search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
    - only send if low/normal EPO level
- ferritin (iron deficiency can mask the diagnosis; if iron deficient with reticulocytosis, suggestive of PV)

Treatment

- if primary: see *Polycythemia Vera, H43*
- if secondary: treat underlying cause
  - O2 for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours, counselling and education (e.g. smoking cessation, work environment), use the lowest dose possible if on androgen therapy
  - often cardiologists will be hesitant to treat high Hct in cyanotic patients

Thrombocytopenia

Definition

- platelet count <150 x 10^9/L

Clinical Features

- history: mucocutaneous bleeding (easy bruising, gingival bleeding), epistaxis, perioperative bleeding (including dental procedures), heavy menstrual bleeding, peripartum bleeding, and GI bleeding
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura, and wet purpura
- see *Disorders of Primary Hemostasis, H28* for complications

Investigations

- CBC and differential
- blood film
  - rule out pseudothrombocytopenia (platelet clumping or platelet satellitism)
  - decreased production: other cell line abnormalities, blasts (suggesting myeloid malignancy), hypersegmented PMNs (suggesting megaloblastic anemia), and leukoerythroblastic changes (suggesting BM infiltration or fibrosis)
  - increased destruction: large platelets (often seen in ITP), schistocytes (seen in MAHA/TMA)
- workup for nutritional deficiencies: B12, RBC, folate
- PT/INR, aPTT, and fibrinogen if DIC suspected
- LFTs if findings of liver disease are present
- *H. pylori*, HIV, and HCV serology
- abdominal U/S to look for splenomegaly

Rule-of-thumb: a deficit in all cell lines suggests decreased production, sequestration, or hemodilution. A deficit in platelets and RBCs suggests non-immune destruction or Evan's syndrome. An isolated thrombocytopenia suggests an immune-mediated process. In hospitalized patients, drugs and infection account for the majority of cases of thrombocytopenia

Rule out pseudothrombocytopenia: platelet clumping secondary to EDTA Abs present in serum. This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA)

Wet vs. Dry Purpura
Wet purpura: hemorrhage of mucous membranes
Dry purpura: bruising or petechiae on skin surface

Treatments
- life-threatening bleeding: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see *Immune Thrombocytopenia, H28*

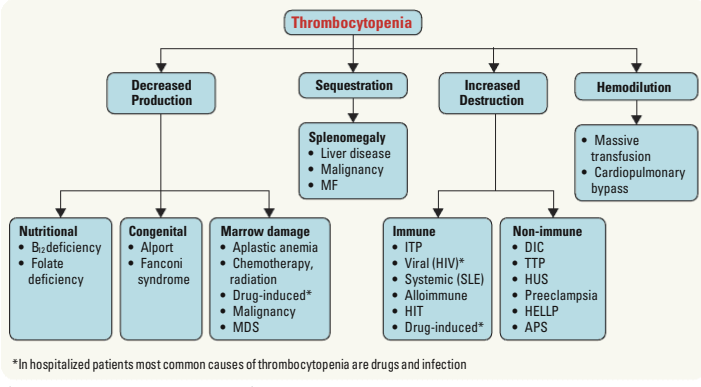

Figure 3. Approach to thrombocytopenia
Adapted from: Cecil Essentials of Medicine

References
APS: see *Hematology, H36*
Aplastic Anemia: see *Hematology, H17*
B12/Folate Deficiency: see *Hematology, H25, H26*
DIC: see *Hematology, H34*
HIT: see *Hematology, H30*
HIV: see Infectious Diseases, ID27
ITP: see *Hematology, H28*
Myelodysplasia: see *Hematology, H41*
Preeclampsia: see Obstetrics, OB26
SLE: see Rheumatology, RH11

Thrombocytosis

Definition
- platelet count >450 x 10^9/L
- primary thrombocytosis (uncommon): due to MPNs (e.g. CML, PV, primary MF, and ET; rarely associated with MDS)
- reactive/secondary thrombocytosis (common): acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasm, ischemic injury, and hyposplenia/asplenia)

Clinical Features
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, and constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, and aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly is a common finding among patients with MPNs

Investigations
- CBC and differential, peripheral blood film, serum ferritin
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, BM biopsy may be required to rule out MPN/MDS

Treatment
- primary: Aspirin™ ± cytoreductive agents (e.g. hydroxyurea, anagrelide, interferon-α)
- secondary: treat underlying cause

Pancytopenia

Definition
- a decrease in all hematopoietic cell lines below normal reference ranges

Clinical Features
- anemia: fatigue (see *Anemia, H6*)
- leukopenia: recurrent infections (see *Neutropenia, H9*)
- thrombocytopenia: mucocutaneous bleeding (see *Thrombocytopenia, H7*)

Investigations
- CBC and differential, peripheral blood film, serum ferritin, reticulocyte count, PT, PTT, blood type and screen, complete metabolic panel, B_{12}, folate
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- workup as per *Figure 4, H9* and presenting symptoms/physical exam
- if reactive process has been ruled out, BM biopsy may be required

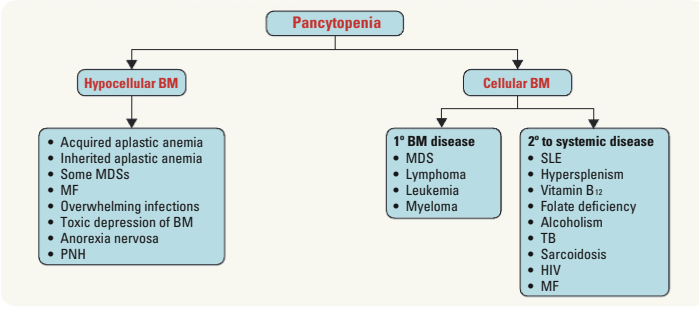

Figure 4. Approach to pancytopenia

Neutrophilia

Definition
- variable definition, but generally an ANC >7.7 x 10^9/L (WHO definition)

Etiology
- primary neutrophilia
  - CML, chronic neutrophilic leukemia
  - other MPNs: PV, ET, MF
  - hereditary neutrophilia (autosomal dominant)
  - chronic idiopathic neutrophilia in otherwise healthy patients
  - leukocyte adhesion deficiency
- secondary neutrophilia
  - stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  - obesity
  - infection
  - inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, and burns
  - malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  - medications: glucocorticoids, β-agonists, lithium, G-CSF

Clinical Features
- signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  - including LAD and organomegaly
- examine oral cavity, teeth, peri-rectal area, genitals, and skin for signs of infection

Investigations
- CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
- blood film: left shifted WBCs, Döhle bodies (intracytoplasmic structures composed of agglutinated ribosomes), toxic granulation, and cytoplasmic vacuoles in infection
- may require BM biopsy if MPN suspected

Treatment
- directed at underlying cause

Neutropenia

Definition
- mild: ANC 1.0-1.5 x 10^9/L
- moderate: ANC 0.5-1.0 x 10^9/L (risk of infection starts to increase)
- severe: ANC <0.5 x 10^9/L
- profound: ANC <0.1 x 10^9/L for >7 d

ANC Calculation
ANC = WBC count x (%PMNs + %bands)
Beware of fever + ANC <0.5 x 10^9/L = FEBRILE NEUTROPENIA

Etiology

Table 6. Etiology of Neutropenia

Decreased Production	Peripheral Destruction/Sequestration	Excessive Margination (Transient Neutropenia)
Infection Viral hepatitis, EBV, HIV, TB, typhoid, malaria **Hematological Diseases** Idiopathic, aplastic anemia, MF, BM infiltration, cyclic, PNH, MDS, large granular lymphocyte leukemia, hairy cell leukemia, immune-mediated **Drug-Induced** Alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, antithyroid drugs **Toxins/Chemicals** High dose radiation, benzene, dichloro diphenyl trichloroethane (DDT) **Nutritional Deficiency** B 12, folate **Idiopathic** Constitutional neutropenia, benign cyclic neutropenia	Anti-neutrophil Abs Spleen or lung trapping Autoimmune disorders: RA (Felty syndrome), SLE Granulomatosis with polyangiitis (formerly Wegener's) Drugs: haptens (e.g. α-methyldopa)	Idiopathic (most common) Overwhelming bacterial infection Hemodialysis Cardiopulmonary bypass Racial variation (e.g. African or Ashkenazi Jewish descent)

Prophylactic Hematopoietic Colony-Stimulating Factors on Mortality and Infection
Ann Intern Med 2007;147:400-411
Purpose: To review the effects of colony-stimulating factor (CSF) on mortality, infections, and febrile neutropenia in patients undergoing chemotherapy or SCT.
Study Selection: 148 RCTs comparing the effects of CSFs to either placebo or no therapy were included. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.
Results: There were no differences in all-cause mortality or infection-related death between CSF and placebo groups. Compared to placebo or no therapy, CSFs reduced infection rate (median rate 38.9% vs. 43.1%; rate ratio 0.85), microbiologically documented infections (MR 23.5% vs. 28.6%; rate ratio 0.86), and febrile neutropenia (MR 25.3% vs. 44.2%; rate ratio 0.71).
Conclusions: Prophylactic CSFs decrease infection rates and episodes of febrile neutropenia in patients undergoing chemotherapy or SCT, but have no effect on mortality.

Clinical Features
- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. *S. aureus*, Gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth, and throat following colonization by opportunistic organisms
- avoid digital rectal exam

Investigations
- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs and differential with peripheral smears to BM aspiration and biopsy

Treatment
- manage specific underlying causes and medications that contribute to neutropenia
- regular dental care: chronic gingivitis and recurrent stomatitis are major sources of morbidity
- treatment of febrile neutropenia
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, and methotrexate)

G-CSF = Neupogen® = filgrastim

Lymphocytosis

Definition
- absolute lymphocyte count >4.0 x 10^9/L

Etiology
- infection (reactive lymphocytosis)
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
- smoking
- physiologic response to stress (e.g. trauma, status epilepticus)
- hypersensitivity (e.g. drugs, serum sickness)
- autoimmune (e.g. RA)
- neoplasm (e.g. CLL, thymoma, B-cell lymphocytosis of undetermined significance)
- asplenia (e.g. post-splenectomy)

Presence of atypical lymphocytes suggests viral infection

Presence of smudge cells suggests a lymphoproliferative disorder if persistently elevated above 5.0 x 10^9/L for >3 mo; consider flow cytometry of peripheral blood

Investigations
- CBC and differential, peripheral smear assessing lymphocyte morphology, and in select cases, flow cytometry for assessing lineage and clonality

Treatment
- treat underlying cause

Lymphopenia

Definition
- absolute lymphocyte count <1.0 x 10^9/L

Etiology
- older age
- idiopathic CD4+ lymphopenia
- iatrogenic (radiation, chemotherapy, immunosuppressive agents)
- HIV/AIDS, HBV, HCV
- malignancy
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)

Clinical Features
- opportunistic infections (see Infectious Diseases, ID29)

Investigations
- CBC and differential, lymphocyte subpopulations, immunoglobulin levels

Treatment
- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see Infectious Diseases, ID29)

Eosinophilia

Definition
- absolute eosinophil count >0.5 x 10^9/L

Etiology
- primary: due to clonal BM disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome (HES)
    - hypereosinophilia (absolute eosinophil count >1.5 x 10^9/L in the peripheral blood on 2 exams separated by ≥1 mo), with end-organ damage and no other identifiable cause
    - can involve heart, BM, and CNS
- secondary
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes:
    - collagen vascular diseases (e.g. RA, polyarteritis nodosa, see Rheumatology, RH8)
    - respiratory causes (asthma, eosinophilic pneumonia, and eosinophilic granulomatosis with polyangiitis (EGPA))
    - cholesterol emboli
    - hematologic malignancy (myeloid and lymphoid variants), see *Chronic Myeloid Leukemia, H42* and *Hodgkin Lymphoma, H47*
    - adrenocortical insufficiency, see Endocrinology, E39
    - medications (penicillins)
    - atopic dermatitis

Basophilia and/or Eosinophilia
Can be an indicator of CML or other MPNs, associated with pruritus due to excessive histamine production

Investigations
- CBC and differential, peripheral smear assessing eosinophil morphology
- end organ involvement: electrolytes, renal function tests, LFTs, creatine kinase (CK), troponin, ECG, ECHO, pulmonary function tests (PFTs), CXR, chest and abdominal CT, consider BM biopsy

Treatment
- treat underlying cause
- before initiating steroids, ensure strongyloides serology is collected to rule out infection for patients at risk

Agranulocytosis

Definition
- ANC is <100/μL

Etiology
- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine, and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced Abs or direct toxic effects upon marrow granulocytic precursors

Clinical Features
- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

Prognosis
- high fatality without vigorous treatment

Investigations/Treatment
- discontinue offending drug
- if patient is febrile, pan-culture and screen for infection (blood cultures x2, urine culture, and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider BM aspirate and biopsy if cause unclear
- consider G-CSF

Leukemoid Reaction

Definition
- leukocytosis >50 x 10^9/L

Etiology
- infection
- drugs
- asplenia
- intoxication
- malignancy
- hemorrhage
- acute hemolysis

Investigations/Treatment
- marked left shift (myelocytes, metamyelocytes, and bands in peripheral blood smear)
- rule out CML and chronic neutrophilic leukemia
- detect and treat underlying cause

Approach to Lymphadenopathy

History
- constitutional/B-symptoms (seen in TB, lymphoma, other malignancies)
- growth pattern: acute vs. chronic
- exposures: cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), and high-risk behaviours (HIV)
- joint pain/swelling, rashes (connective tissue disorder)
- pruritus (seen in Hodgkin lymphoma)
- medications (can cause serum sickness → lymphadenopathy)

Constitutional/B-Symptoms

Unexplained temperature >38°C

Unexplained weight loss (>10% of body weight in 6 mo)

Night sweats

Clinical Features
- determine if lymphadenopathy is localized or generalized
- generalized: typically features of systemic diseases (HIV, TB, EBV, SLE, medications, sarcoidosis, lymphoma)
- localized: typically reactive or neoplastic
  - cervical (bacterial/mycobacterial infections, ENT malignancies, and metastatic cancer)
  - supraclavicular (highest malignancy risk)
    - right (mediastinal, bronchogenic, esophageal cancer)
    - left (gastric, gallbladder, pancreas, renal, and testicular/ovarian cancer)
  - axillary (cat scratch fever, breast cancer, and metastatic cancer)
  - epitrochlear (infections, sarcoidosis, and lymphoma)
- check for splenomegaly, constitutional symptoms

Lymphadenopathy-Causing Drugs
- Allopurinol
- Atenolol
- Captopril
- Carbamazepine
- Cephalosporins
- Gold
- Hydralazine
- Penicillin
- Phenytoin
- Primidone
- Pyrimethamine
- Quinidine
- Sulfonamides
- Sulindac

Investigations
- CBC and differential, blood film
- if generalized, consider tuberculin test, HIV RNA, VDRL, Monospot*/EBV serology, antinuclear antibodies (ANA), and imaging
- if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → excisional biopsy to preserve lymph node architecture)
- in areas difficult to access (retroperitoneal, mediastinal/hilar), multiple core biopsies may be more practical/feasible
- FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (excisional biopsy is the gold standard)
  - FNA is helpful for recurrence of solid tumour malignancy

Table 7. Inflammatory vs. Neoplastic Lymph Nodes

Feature	Inflammatory	Neoplastic
Consistency	Fluctuant/soft	Firm/hard
Mobility	Mobile	Matted/immobile
Tenderness	Tender	Non-tender
Size	<1 cm*	>1 cm*

Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender
*Note: inguinal lymph nodes can be up to 2 cm in size and non-pathologic

Table 8. Differential Diagnosis of Generalized Lymphadenopathy

Reactive	Inflammatory	Neoplastic
Bacterial (TB, Lyme, brucellosis, cat scratch disease, and syphilis)	Collagen disease (RA, dermatomyositis, SLE, vasculitis, and Sjögren's)	Lymphoproliferative disorder
Viral (EBV, CMV, HIV)	Drug hypersensitivity	Metastatic cancer
Parasitic (toxoplasmosis)	Sarcoidosis, amyloidosis	Histiocytosis X
Fungal (histoplasmosis)	Serum sickness	

Approach to Splenomegaly

Table 9. Differential Diagnosis of Splenomegaly

Increased Demand for Splenic Function			Congestive	Infiltrative
Hematological	**Infectious**	**Inflammatory**	**Cirrhosis**	**Non-Malignant**
Nutritional anemias	Viral e.g. EBV, HIV/ AIDS, CMV	SLE	Portal HTN	Benign metaplasia
Hemoglobinopathies	Bacterial e.g. bacterial endocarditis, TB	Sarcoidosis	Portal vein obstruction (including right heart failure)	Cysts
Hemolysis	Parasitic e.g. malaria, histoplasmosis, leishmaniasis	Felty syndrome	Splenic vein thrombosis	Amyloidosis
Spherocytosis	Fungal	Still's disease		Sarcoidosis
Sequestration crisis				Hamartomas
Elliptocytosis				Vascular abnormalities
				Lysosomal storage diseases (Gaucher's, Niemann-Pick)
				Glycogen storage diseases
				Malignant
				Leukemia (CML, CLL)
				Lymphoproliferative disease (CLL, NHL/HL)
				MPNs (CML, MF)
				Metastatic tumour

The underlined conditions cause massive splenomegaly (spleen crosses midline or reaches pelvis)

Causes of Splenomegaly

CHINA
Cirrhosis/Congestion (portal HTN)
Hematological
Infectious
Neoplasm
Autoimmune

History
- constitutional/B symptoms, feeling of fullness in LUQ, and early satiety
- signs or symptoms of infection (e.g. mononucleosis) or malignancy
- history of liver disease, hemolytic anemia, or high-risk exposures

Clinical Features
- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell's sign, Traube's space, and Nixon's method) and palpation
- associated LAD or hepatomegaly
- signs of CHF

Investigations
- CBC and differential, blood film
- as indicated: liver enzymes (AST, ALT, ALP, and GGT) and/or LFTs (platelet, INR, albumin, and bilirubin), reticulocyte count, Monospot*/EBV, haptoglobin, LDH, infectious and autoimmune workup, and BM biopsy/aspirate when malignancy suspected
- imaging
  - ultrasound of abdomen/liver to assess for cirrhosis and portal vein thrombosis (if positive, refer to hepatology)
  - echo for cardiac function
  - CT to rule out lymphoma and assess splenic lesions

Microcytic Anemia

- MCV <80 fL
- see *Figure 2, H6*

Table 10. Iron Indices and Blood Film in Microcytic Anemia

	Lab Tests					Blood Film
	Ferritin	Serum Iron	TIBC	% saturation	RDW	
Iron Deficiency Anemia	↓↓	↓	↑	↓	↑ (>15)	Hypochromic, microcytic
Anemia of Chronic Disease	N/↑	↓	↓	N	N	Normocytic/microcytic
Sideroblastic Anemia	N/↑	↑	N	N/↑	↑	Dual population Basophilic stippling
Thalassemia	N/↑	N/↑	N	N/↑	N/↑	Hypochromic, microcytic Basophilic stippling Poikilocytosis

Causes of Microcytic Anemia

TAILS
Thalassemia
Anemia of chronic disease/ inflammation
Iron deficiency
Lead poisoning
Sideroblastic anemia

Iron Metabolism

Iron Intake (Dietary)
- average North American adult diet = 10-20 mg iron daily
- steady state absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid and ascorbic acid (vitamin C); reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males more likely to have positive iron balance; up to 20% of menstruating females have negative iron balance

Iron Absorption and Transport
- dietary iron is absorbed in the duodenum (absorption impaired in IBD and celiac disease)
- in circulation, the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages of the reticuloendothelial system and hepatocytes) to RBC precursors in the BM

Iron Levels
- hepcidin is a hormone produced by hepatocytes that regulates systemic iron levels
  - binds to iron exporter ferroportin (on duodenal enterocytes and reticuloendothelial cells) and induces its degradation, thereby inhibiting iron export into circulation (iron trapping in reticuloendothelial system cells and diminished absorption of iron)
  - hepcidin production is
    - increased in states of iron overload (inhibiting additional iron absorption) and inflammation (mediating anemia of chronic disease through iron trapping)
    - decreased in states where erythropoiesis is increased (e.g. hemolysis) or oxygen tension is low

Iron Storage
- ferritin
  - ferric iron (Fe^{3+}) complexed to a protein called apoferritin (liver, spleen, and BM are main ferritin storage sites)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated to some extent despite low iron stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is the main source of hemosiderin storage

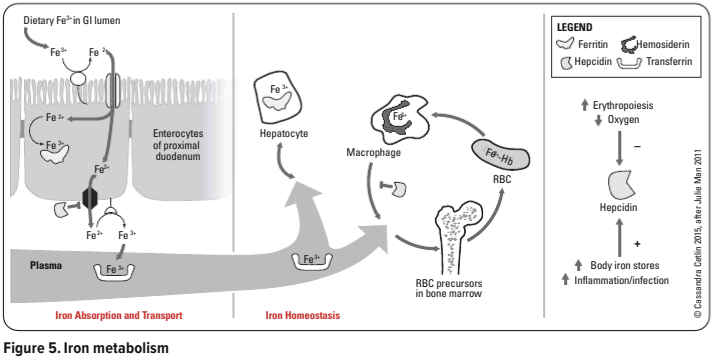

Figure 5. Iron metabolism

Iron Indices

- BM aspirate: gold standard test for assessment of iron stores (rarely done for this indication)
- serum ferritin: most important blood test for measuring iron stores
  - decreased in iron deficiency anemia
  - elevated in infection, inflammation, malignancy, liver disease, hyperthyroidism, and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
- TIBC: indirect measure of total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - increased TIBC has high specificity for decreased iron, low sensitivity
- transferrin saturation
  - serum iron divided by TIBC, expressed as a proportion or a percentage
- sTfR
  - reflects functional availability of iron at the tissue level
  - transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some are cleaved off and are present in circulation as sTfR
  - in iron deficient states, more transferrin receptors are expressed on erythroblasts leading to an

increase in sTfR
- sTfR also increased during extramedullary hematopoiesis (i.e. thalassemia syndromes)
- low in reduced erythropoiesis and iron overload
- useful in identifying iron deficiency in the setting of chronic inflammatory disorders (where ferritin levels can be elevated though iron stores are low; see *Iron Deficiency Anemia, H15*)

Iron Deficiency Anemia

- see Pediatrics, P51
- most common cause of anemia in North America

Etiology
- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology in the developed world)
  - cow's milk (infant diet), "tea and toast" diet (elderly), absorption imbalances, post-gastrectomy, malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis, and *H. pylori* infection)
- increased losses
  - hemorrhage
    - obvious causes: abnormal uterine bleeding, GI bleed
    - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - chronic intravascular hemolysis (e.g. PNH, cardiac valve RBC fragmentation)

Plummer-Vinson Syndrome
- Dysphagia (esophageal)
- Glossitis
- Iron deficiency anemia
- Stomatitis

Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.)
In males and in post-menopausal women, a GI workup is always warranted (gastroscopy, colonoscopy)

Clinical Features
- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see *Anemia, H6*
- brittle hair, nail changes (brittle, koilonychia)
- pica (appetite for non-food substances, e.g. ice, paint, and dirt)
- restless leg syndrome

Investigations
- CBC, reticulocyte count, blood film, ferritin
  - low ferritin (<30 µg/L) is diagnostic of iron deficiency
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup - complete iron indices, consider sTfR (if available)
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms (oval-shaped RBCs)
  - anisocytosis (RBCs with irregular sharp projections)
  - target cells (RBCs with thicker cell membranes)
- BM aspirate (gold standard, but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation

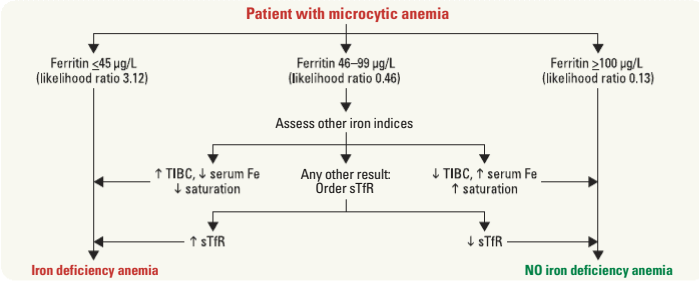

Figure 6. Approach to interpreting iron indices
Adapted from: Am Fam Physician 2007;75:671-678

Treatment
- treat underlying cause
- iron supplementation
  - oral (capsules, syrup)
    - ferrous sulphate 325 mg once daily (65 mg elemental iron), ferrous gluconate 300 mg once daily (35 mg elemental iron), or ferrous fumarate 300 mg once daily (100 mg elemental iron), polysaccharide iron complex (150 mg elemental iron), heme iron polypeptide (11 mg elemental iron)
    - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - recent studies demonstrate alternate day dosing may be non-inferior to daily or more frequent dosing, due to improved absorption, though this is still an area of investigation
    - there is no role for dosing oral iron more than once-daily; this results in hepcidin up-regulation and decreased absorption (and more side effects without clinical benefit)
  - IV iron can be considered if patient cannot tolerate or absorb oral iron, and/or if there is a need for quick recovery (e.g. chronic bleeding not manageable with oral iron)
- monitoring response
  - reticulocyte count will begin to increase after one wk
  - Hb increases by 10 g/L per wk (if no blood loss)

Anemia of Chronic Disease

(Also known as anemia of inflammation)

Etiology
- infection, malignancy, inflammatory, and rheumatologic disease
- chronic renal and liver disease
- endocrine disorders (e.g. diabetes mellitus, hypothyroidism, hypogonadism, and hypopituitarism)

Pathophysiology
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - hepatic hepcidin production is increased in inflammatory processes, trapping iron in enterocytes and macrophages (via ferroportin inhibition), see *Figure 5, H14*
  - reduced plasma iron levels make iron relatively unavailable for new Hb synthesis
  - marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present i.e. RBC survival is modestly decreased

Investigations
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen, and platelets)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- "classic" serum iron indices: see *Table 10, H14*
- BM
  - normal or increased iron stores
  - decreased or absent staining for iron in erythroid precursors

Treatment
- treat underlying disease; only treat in patients who would benefit from a higher Hb
- IV iron if no benefit from PO iron (overcomes sequestration in enterocytes) or with use of ESAs in CKD
- EPO indicated in chronic renal failure; ensure Hb target <110 g/L (increased risk of vascular events/ischemic stroke with higher Hb targets)

Sideroblastic Anemia

- uncommon compared to iron deficiency anemia or anemia of chronic disease

Sideroblasts
- erythrocytes with small coarse or fine blue iron-containing (basophilic) granules in the cytoplasm
- "normal": granules are small and randomly spread in the cytoplasm
- "ring": iron deposits in mitochondria, forming large, abnormal granules that surround the nucleus
  - hallmark of sideroblastic anemia

Etiology
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - refractory anemia with ringed sideroblasts: a subtype of MDS (see *Myelodysplastic Syndromes, H41*)
  - may be a preleukemic phenomenon (1-2% transform to AML)
- reversible
  - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, and hypothyroidism

Clinical Features
- anemia symptoms (see *Anemia, H6*)
- hepatosplenomegaly

Investigations
- serum iron indices: see *Table 10, H14*
- CBC and blood film
  - ring sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikilocytosis (abnormally shaped RBCs), basophilic stippling
- BM biopsy

Treatment
- depends on etiology
  - X-linked: high dose pyridoxine (vitamin B_6) in some cases
  - acquired: EPO and G-CSF
  - reversible: remove precipitating cause
- supportive transfusions for severe anemia
- monitor for iron overload driven by ineffective erythropoiesis and/or transfusion

Lead Poisoning

Definition/Etiology
- blood lead levels >80 µg/dL, may be symptomatic at 50 µg/dL
- identify source: consider occupational history, exposures history, and utensil history

Clinical Features
- pallor, abdominal pain, constipation, irritability, and difficulty concentrating

Treatment
- chelation therapy: dimercaprol and EDTA are first line agents

Consider lead poisoning in any child with microcytic anemia who lives in a house built before 1977

Features of Lead Poisoning

LEAD
Lead lines on gingivae and epiphyses of long bones on x-ray
Encephalopathy and Erythrocyte basophilic stippling
Abdominal colic and microcytic Anemia (sideroblastic)
Drops (wrist and foot drop)

Normocytic Anemia

- MCV 80-100 fL
- see *Figure 2, H6*

Aplastic Anemia

Definition
- destruction of hematopoietic cells of the BM leading to pancytopenia and hypocellular BM

Causes of Normocytic Anemia

ABCD
Acute blood loss
BM failure
Chronic disease
Destruction (hemolysis)

Etiology

Table 11. Etiology of Aplastic Anemia

Congenital	Acquired	
Fanconi syndrome Shwachman-Diamond syndrome Telomeropathies (dyskeratosis congenita)	**Idiopathic** Often T-cell mediated **Drugs** Dose-related (i.e. chemotherapeutics) Idiosyncratic (chloramphenicol, antimalarials, and phenylbutazone) **Toxins** Benzene/organic solvents, DDT, insecticides	**Ionizing Radiation** **Post-Viral Infection** Parvovirus B19, EBV, HDV, HEV, HBV, HHV6, HIV **Autoimmune (rare)** SLE, Graft-versus-host disease Others PNH, pregnancy, anorexia nervosa, and thymoma

Clinical Features
- can present acutely or insidiously
- symptoms of anemia (see *Anemia, H6*), thrombocytopenia (see *Thrombocytopenia, H7*), and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)

Investigations
- exclude other causes of pancytopenia (see *Figure 4, H9*), including PNH (50% of aplastic anemia patients have PNH+ stem cell clones)
- CBC
  - anemia, neutropenia, or thrombocytopenia (any combination including pancytopenia)
  - decreased reticulocytes (<1% of the total RBC count)
- blood film
  - decreased number of normal RBCs
- BM aspirate and biopsy
  - aplasia or hypoplasia of cells with adipose tissue replacement
  - no evidence of infiltration with malignant cells or fibrosis

Treatment
- remove offending agents
- supportive care (RBC and platelet transfusions, antibiotics)
  - judicious use of blood products to decrease the risk of immune sensitization
  - iron chelation therapy for iron overload (accumulation of iron after multiple >20-unit RBC transfusions)
- immunosuppressive therapy (for idiopathic aplastic anemia)
  - horse or rabbit anti-thymocyte globulin: 40-50% of patients respond
  - cyclosporine (for improved response and survival)
- allogeneic BM transplant
- eltrombopag (TPO receptor agonist) shown to be effective; G-CSF and EPO not effective

Hemolytic Anemia

Definition
- anemia due to destruction and consequently shortened survival of circulating RBCs, usually defined as <100 d
- uncommon cause for anemia (<5% of cases) with many etiologies (>200)

Classification
- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal Hb synthesis (hemoglobinopathies)
- acquired
  - immune
    - autoimmune: warm vs. cold AIHA, see *Table 14, Classification of AIHA, H23*
    - alloimmune: hemolytic disease of the fetus/newborn and post-transfusion
  - non-immune
    - TMA (includes MAHA): thrombus in blood vessel causes RBCs to be sheared – associated with DIC, HUS, aHUS, TTP, preeclampsia/HELLP, vasculitis, and malignant hypertension
    - other causes: PNH, hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, and mechanical heart valves
- also classified as intravascular or extravascular
  - intravascular: TMA and PNH (complement mediated)
  - extravascular: RBCs are coated with Abs (AIHA) or have an abnormal membrane structure/shape or inclusions
  - infections can cause intravascular (*Clostridium*), extravascular, or both (malaria)

On blood film, schistocytes reflect an intravascular hemolysis while spherocytes usually reflect an extravascular hemolysis

Disruption of the heme biosynthetic pathway causes **porphyria**

Porphyria
Inherited or acquired disorders of defective heme synthesis leading to accumulation of porphyrin precursors. Typically presents with non-specific clinical findings (abdominal pain, peripheral neuropathy, neuropsychiatric changes, and/or cutaneous photosensitivity)

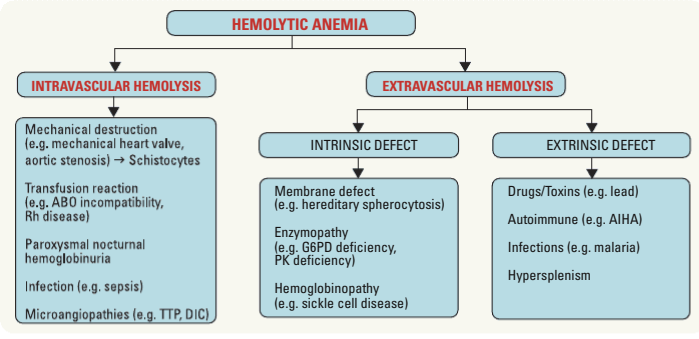

Figure 7. Hemolytic anemia

Heme Breakdown

Heme
↓ Heme oxygenase
Biliverdin
↓ Biliverdin reductase
Bilirubin

Haptoglobin is a circulating protein that mops up free Hb, allowing its clearance in the spleen; when free Hb is abundant, haptoglobin levels decrease

Clinical Features

- jaundice
- dark urine (hemoglobinuria, bilirubinuria)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

Table 12. Investigations for Hemolytic Anemia

Screening Tests	Tests Specific For Intravascular Hemolysis
Increased LDH	Schistocytes on blood film (MAHA)
Decreased haptoglobin	Free Hb in serum
Increased unconjugated bilirubin	Methaemalbuminaemia (heme + albumin)
Increased urobilinogen	Hemoglobinuria (immediate)
Reticulocytosis	Hemosiderinuria (delayed) – most sensitive
Tests Specific for Extravascular Hemolysis	
Direct Antiglobulin Test (direct Coombs) Detects IgG or complement on the surface of RBC Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction	
Indirect Antiglobulin Test (indirect Coombs) Detects Abs in serum that can recognize antigens on RBCs Mix patient's serum + donor RBCs + Coombs serum (anti-human Ig Ab); positive if agglutination Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA	

Thalassemia

Definition

- defects in production of the α or β chains of Hb
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
- clinical manifestations and treatment depend on specific gene and number of alleles affected
- common features
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film
  - CBC: low MCV, low Hb, high RBC count, ± high reticulocyte count

Thalas"SEA"mia

β-thalassemia → more prevalent in Mediterranean
α-thalassemia → more prevalent in South East Asia (SEA) and Africa
(α = Asia, Africa)

Pathophysiology

- defect may be in any of the Hb genes
  - normally 4 α genes in total; 2 on each copy of chromosome 16
  - normally 2 β genes in total; 1 on each copy of chromosome 11
  - fetal Hb, HbF ($\alpha_2\gamma_2$), switches to adult forms HbA ($\alpha_2\beta_2$) and HbA2 ($\alpha_2\delta_2$) at age 3-6 mo
  - HbA constitutes 97% of adult Hb
  - HbA2 constitutes 3% of adult Hb

β-Thalassemia Minor (Thalassemia Trait)

Definition
- defect in single allele of β gene (heterozygous for one normal β globin allele and one β globin thalassemia allele)
- common in people of Mediterranean and South Asian descent

Clinical Features
- usually asymptomatic; a palpable spleen is very rare

Investigations
- Hb (100-140 g/L), MCV (<70 fL), Fe (normal), RBC count (normal/high)
- peripheral blood film – microcytosis, basophilic stippling
- Hb electrophoresis
  - specific: HbA2 increased to 3.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

Treatment
- no treatment required
- genetic counselling for patient and family

Microcytosis in β-Thalassemia Minor
Microcytosis is more profound and the anemia is much milder than that of iron deficiency

β-Thalassemia Major

Definition
- defect in both alleles of β gene (homozygous, autosomal recessive)

Pathophysiology
- ineffective chain synthesis leading to decreased erythropoiesis, hemolysis of RBCs, and increase in HbF

Clinical Features
- initial presentation at age 6-12 mo when HbA (α_2/β_2) normally replaces HbF (α_2/γ_2)
  - severe anemia, jaundice
- iron overload due to compensatory gastrointestinal iron uptake progressing to hemochromatosis
  - secondary to repeated transfusions and ineffective erythropoiesis (through an erythroferrone-mediated mechanism)
  - results in iron-induced organ damage
- stunted growth and development (due to hypogonadism)
- gross hepatosplenomegaly (due to extramedullary hematopoiesis)
- radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
  - skull x-ray has "hair-on-end" appearance
  - pathologic fractures common
- evidence of increased Hb catabolism (e.g. pigmented gallstones)
- death can result from:
  - untreated anemia (should transfuse)
  - infection (should identify and treat early)
  - iron overload (common, late complication)

Hemochromatosis Clinical Features

ABCDH
Arthralgia
Bronze skin
Cardiomyopathy, Cirrhosis of liver
Diabetes (pancreatic damage)
Hypogonadism (anterior pituitary damage)

Investigations
- CBC and iron studies
- severe microcytic anemia (Hb <60 g/L)
- peripheral blood film: teardrop, target, hypochromic, microcytic
- Hb electrophoresis
  - HbA: 0-10% (normal >95%)
  - HbA2 >2.5%
  - HbF: 90-100%

Treatment
- life-long regular RBC transfusions to suppress endogenous erythropoiesis
- iron chelation (e.g. deferoxamine, deferasirox, and deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)
- folic acid supplementation if not transfused
- allogeneic BM transplantation (potentially curative) or cord blood transplant
- gene therapy (to encode adult Hb A) or CRISPR-Cas 9 gene editing (to allow for increased HbF production) under study
- splenectomy (now performed less frequently)

β-Thalassemia Intermedia

Definition
- clinical diagnosis in patients whose clinical manifestations are too mild to be classified as β-thalassemia major, but too severe to be classified as β-thalassemia minor

Clinical Features
- wide variety of clinical phenotypes
- in most cases of β-thalassemia intermedia, both β-globin genes are affected
- three main mechanisms account for the milder phenotype compared to β-thalassemia major: (1) subnormal (vs. absent) β-chain synthesis, (2) increased number of γ chains, and (3) coinheritance of α-thalassemia (in some cases)
- complications more commonly seen in β-thalassemia intermedia than β-thalassemia major include extramedullary hematopoiesis, leg ulcers, gallstones, thrombosis, pulmonary hypertension, and growth retardation

Treatment
- most patients only require periodic transfusions, although regular transfusions may eventually be necessary in adulthood (third to fourth decade of life)
- folic acid supplementation if not transfused
- iron chelation therapy may be needed to mitigate iron overload from ineffective erythropoiesis and subsequent hepcidin downregulation via erythroferrone; can assess liver iron concentration (LIC) with an MRI, chelation should be considered if LIC >5 mg/g

α-Thalassemia

Definition
- defect(s) in α genes
- similar geographic distribution as β-thalassemia, but higher frequency among Southeast Asians and Africans

Clinical Features
- 1 defective α gene (aa/a-): clinically silent; normal Hb, normal MCV
- 2 defective α genes (cis: aa/-- or trans: a-/a-): normal Hb, decreased MCV
  - N.B. cis 2-gene deletion more common in Asia vs. trans 2-gene deletion more common in Africa – this leads to increased risk of fetal hydrops in offspring of patients from Southeast Asia vs. Africa
- 3 defective α genes (a-/--): HbH (β4) disease; presents in adults, decreased Hb, decreased MCV, and splenomegaly
- 4 defective α genes (--/--): Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

Investigations
- CBC and iron studies (for iron overload)
- peripheral blood film – screen for HbH inclusion bodies with supravital stain
- Hb electrophoresis can be used to identify HbH disease, but may miss 1- or 2-gene deletions; definitive diagnosis with DNA genotyping

Treatment
- referral for genetic/prenatal counselling
- depends on degree of anemia
  - 1 or 2 defective α genes: no treatment required
  - HbH disease: similar to β-thalassemia intermedia
  - Hb Barts: no definitive treatment
    - majority of pregnancies terminated (fetal/maternal mortality risk)
    - intrauterine transfusion, stem cell transplants

Sickle Cell Disease

Definition
- autosomal recessive sickling disorders are most commonly caused by a Glu → Val substitution at position 6 of the β-globin chain (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)
  - increased incidence of HbS allele in patients with Sub-Saharan African, Indian, Middle Eastern, or Mediterranean heritage (thought to be protective against malaria)
- SCD occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

Pathophysiology
- at low pO_2, deoxyHbS polymerizes leading to rigid crystal-like rods that distort membranes → 'sickles'
- the pO_2 level at which sickling occurs is related to the percentage of HbS present
- sickling is aggravated by acidemia, increased CO_2, increased 2,3-DPG, fever, and increased osmolality
- fragile sickle cells then cause injury in two main ways
  1. fragile sickle cells hemolyze (nitric oxide depletion)
  2. occlusion of small vessels (hypoxia, ischemia-reperfusion injury)

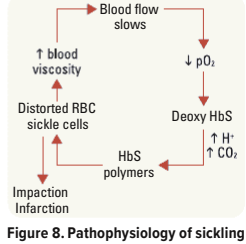

Figure 8. Pathophysiology of sickling

Functional Asplenism: increased susceptibility to infection by encapsulated organisms
- *S. pneumoniae*
- *N. meningitidis*
- *H. influenzae*
- *Salmonella (osteomyelitis)*

Clinical Features

- sickle cell trait (HbAS): asymptomatic except during extreme hypoxia or infection
  - increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - retarded growth and development ± skeletal changes
  - splenomegaly in childhood; splenic atrophy in adulthood
- SCD-SS often presents with acute pain episode
  1. aplastic crises
     - toxins and infections (especially parvovirus B19) transiently suppress BM
  2. splenic sequestration crises
     - usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
     - uncommon in adults due to asplenia from repeated infarction
  3. vaso-occlusive crises (microcirculation infarction)
     - may affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen, and extremities), fever, and leukocytosis
     - can cause a stroke or a silent MI
     - precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses, and alcohol
  4. acute chest syndrome
     - acute illness characterized by fever and/or respiratory symptoms
     - new pulmonary infiltrate on chest x-ray
     - precipitated by pulmonary infection, fat emboli, and pulmonary infarction
- SCD-SC (HbSC): most common compound heterozygote
  - 1 in 833 live births in African-Americans, common in West Africa
  - milder anemia than HbSS
  - similar complications as HbSS but typically milder and less frequent (exception is proliferative sickle cell retinopathy, glomerulonephritis, and avascular necrosis)
  - spleen not always atrophic in adults

Organs Affected by Vaso-Occlusive Crisis

Organ	Problem
Brain	Ischemic or hemorrhagic stroke, vasculopathy
Eye	Hemorrhage, blindness
Liver	Infarcts, RUQ syndrome
Lung	Acute chest syndrome, long-term pulmonary hypertension
Gallbladder	Stones
Heart	Hyperdynamic flow murmurs
Spleen	Enlarged (child); atrophic (adult)
Kidney	Hematuria, loss of renal concentrating ability, proteinuria
Intestines	Acute abdomen
Placenta	Stillbirths
Penis	Priapism
Digits	Dactylitis
Bone	Infarction, infection, avascular necrosis (femoral and humeral head)
Skin	Leg ulcers (ankle)

Investigations

- sickle cell prep (detects sickling of RBCs under the microscope in response to O_2 lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC, and other variants
- all newborns in developed countries typically screened for SCD

Table 13. Investigations for Sickle Cell Disease

	HbAS	HbSS
CBC	Normal	Increased reticulocytes, decreased Hb, and decreased Hct
Peripheral Blood	Normal; possibly a few target cells	Sickled cells
Hb Electrophoresis	HbA fraction of 0.65 (65%) HbS fraction of 0.35 (35%)	No HbA, only HbS and HbF (proportions change with age); normal amount of HbA2

Treatment

- genetic counselling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
  1. folic acid to prevent folate deficiency
  2. hydroxyurea (HU) to enhance production of HbF
     - mechanism of action = stops repression of fetal Hb-γ gene thereby increasing production of stem cells expressing HbF (HbF decreases polymerization and precipitation of HbS in sickle cell RBCs)
     - short-term harms (within 6 mo): dose-related leukopenia, thrombocytopenia, anemia, and decreased reticulocyte count; decreased sperm production, mucositis, skin ulcers
     - long-term harms: potentially birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug
  3. treatment of vaso-occlusive crisis
     - supportive care: oxygen, hydration (reduces viscosity), correct acidosis, analgesics/opiates
     - indication for exchange transfusion: SCD complications (acute chest syndrome, aplastic crises, hepatic or splenic sequestration, and stroke), prevention of complications, preoperative
     - less routinely: antimicrobials for suspected infection
  4. prevention of crises
     - establish diagnosis
     - avoid conditions that promote sickling (hypoxia, acidosis, dehydration, and fever)
     - vaccination in childhood (*S. pneumoniae, N. meningitidis*, and *H. influenzae* type b)
     - prophylactic penicillin (age 3 mo-5 yr)
     - good hygiene, nutrition, and social support

Hydroxyurea (Hydroxycarbamide) for Sickle Cell Disease
Cochrane DB Syst Rev 2017;4:CD002202
Purpose: To assess the effects of hydroxyurea therapy in patients of any age and genotype with sickle cell disease (SCD).
Study Selection: Randomised and quasi-randomised controlled trials ≥1 month comparing hydroxyurea with placebo, standard therapy or other interventions.
Results: 8 RCTs were included, 899 total patients (both adults and children with SCD). When compared to placebo, hydroxyurea was associated with statistically significant improvements in pain alteration (pain crisis frequency, duration, intensity, hospital admissions and opioid use), measures of HbF and neutrophil counts, and fewer occurrences of acute chest syndrome and blood transfusions. Differences in quality of life and adverse events (including serious or life-threatening events) were not statistically significant.
Conclusion: Evidence suggests that hydroxyurea can effectively decrease the frequency of pain episodes and other acute complications in patients with SCD. However, data on the long-term benefits and risks of hydroxyurea is still insufficient.

5. screen for complications
   - regular blood work (CBC, reticulocytes, iron indices, BUN, LFTs, and creatinine)
   - urinalysis annually (proteinuria and glomerulopathy)
   - transcranial doppler annually until 16 yr (stroke prevention)
   - retinal examinations annually from 8 yr (screen for retinopathy)
   - echocardiography once in late childhood/early adulthood (screen for pulmonary hypertension)
6. newer therapies
   - gene therapy
   - voxelotor
   - crizanlizumab

Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)
Blood 2012;119:3925-32
Purpose: To compare standard treatment (transfusions/chelation) to alternative treatment (hydroxyurea/phlebotomy) for children with sickle cell anemia (SCA), stroke, and iron overload.
Methods: 133 pediatric patients were randomized to (1) continuation of monthly erythrocyte transfusions with oral deferasirox (28.2 ± 6.0 mg/kg/d) or (2) initiation on hydroxyurea (20 mg/kg/d escalated to maximum tolerated dose (MTD)=26.2 ± 4.9 mg/kg/d) with discontinuation of transfusions at MTD, and monthly phlebotomy (5-10 mL/kg/mo) for iron overload.
Primary Outcome: Secondary stroke recurrence rate and quantitative liver iron content.
Results: Stroke recurrence rate was significantly lower in patients on transfusions/deferasirox as compared to those initiated on hydroxyurea/phlebotomy (0% vs. 10%, P<0.05). Differences in liver iron content between the two treatment arms were not statistically different (16.6 mg/g dry weight liver in transfusions/deferasirox vs. 15.7 mg/g in hydroxyurea/phlebotomy).
Conclusion: Transfusions and chelation remain the preferred management strategies for pediatric patients with SCA, stroke, and iron overload.

Autoimmune Hemolytic Anemia

Table 14. Classification of AIHA

	Warm (75-90% cases)	Cold
Ab Allotype	IgG	IgM
Agglutination Temperature	37°C	4-37°C
Direct Coombs Test (direct antiglobulin test)	Positive for IgG ± complement	Positive for complement
Etiology	Idiopathic Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin lymphoma) Secondary to autoimmune disease (e.g. SLE) Pregnancy Drug-induced (e.g. penicillin, quinine, methyldopa)	Idiopathic Secondary to infection (e.g. mycoplasma pneumonia, EBV, HCV, syphilis) Secondary to lymphoproliferative disorder (e.g. macroglobulinemia, CLL)
Blood Film	Spherocytes	Agglutination
Management	Treat underlying cause Folic acid Corticosteroids (1st-line) Folic acid Rituximab (2nd-line to steroids) Immunosuppression Splenectomy	Treat underlying cause Folic acid Warm patient/avoid cold Rituximab regimen (1st-line) Plasma exchange (2nd-line for high IgM levels) Low dose alkylating agents (chlorambucil, cyclophosphamide) or interferon may be useful but less effective

Microangiopathic Hemolytic Anemia (MAHA)/Thrombotic Microangiopathy (TMA)

Definition
- hemolytic anemia due to intravascular fragmentation of RBCs

Etiology
- see *Thrombotic Thrombocytopenic Purpura (TTP), H31*
- *see Hemolytic Uremic Syndrome, H31*
- see *Disseminated Intravascular Coagulation, H34*
- eclampsia, HELLP syndrome, AFLP
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic APS

Investigations
- blood film: schistocytes
- hemolytic workup (CBC, reticulocyte count, LDH, haptoglobin, indirect bilirubin)
- Coombs test: negative
- urine: hemosiderinuria, hemoglobinuria

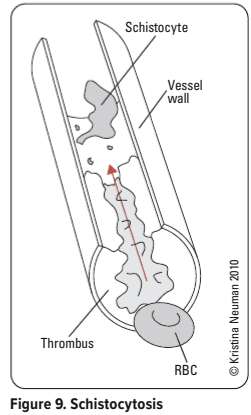

Figure 9. Schistocytosis

Hereditary Spherocytosis

Definition/Etiology
- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
- autosomal dominant (variable penetrance), can also be autosomal recessive or de novo
- presents with hemolytic anemia, jaundice, splenomegaly

Investigations
- CBC and differential blood film (shows spherocytes)
- RBC dehydration and membrane loss result in elevated MCHC
- osmotic fragility (increased)
- molecular analysis for spectrin gene
- U/S (splenomegaly and gallstones (pigment))

Treatment
- genetic counselling
- in severe cases, splenectomy (avoid splenectomy in early childhood); vaccination against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b pre-splenectomy

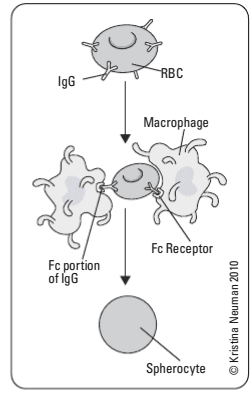

Figure 10. Spherocytosis secondary to AIHA

Hereditary Elliptocytosis

Definition/Etiology
- abnormal interactions between spectrin and other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

Treatment
- genetic counselling
- if severe hemolysis: folate supplementation, immunization, splenectomy

Glucose-6-Phosphate Dehydrogenase Deficiency

Definition/Etiology
- deficiency in G6PD leading to a lack of reduced glutathione and increased RBC sensitivity to oxidative stress
- X-linked recessive, prevalent in individuals of African, Asian, and Mediterranean descent

Clinical Features
- frequently presents as episodic hemolysis precipitated by:
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, and nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

Investigations
- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (clumps of denatured Hb attached to RBC membrane)
  - bite cells (indicative of oxidative hemolysis; generated by passage through spleen)

Treatment
- genetic and prenatal counselling
- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases

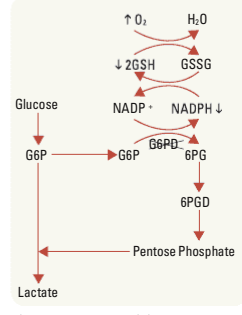

Figure 11. G6PD deficiency

Macrocytic Anemia

- MCV >100 fL
- see *Figure 2, H6*

Table 15. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia

	Megaloblastic	Non-Megaloblastic
Morphology	Large, oval, nucleated RBC precursor Hypersegmented neutrophils	Large round RBC Normal neutrophils
Pathophysiology	Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm	Reflects membrane abnormality with abnormal cholesterol metabolism

Note: MDS is a non-megaloblastic macrocytic anemia that commonly presents with oval macrocytosis

Causes of Macrocytic Anemia

ABCDEF
Alcoholism (liver disease)
B$_{12}$ deficiency
Compensatory reticulocytosis
Drugs (cytotoxic, azidothymidine)/ Dysplasia
Endocrine (hypothyroidism)
Folate deficiency/Fetus (pregnancy)

Characteristics of Megaloblastic Macrocytic Anemia
Pancytopenia
Hypersegmented neutrophils
Megaloblastic BM

Vitamin B$_{12}$ Deficiency

- B$_{12}$ (cobalamin)
- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

Etiology

Table 16. Etiology of Vitamin B$_{12}$ Deficiency

Diet	Gastric	Intestinal Absorption	Genetic
Strict vegan More likely to present in pediatric population Vegetarian in pregnancy Malnutrition	**Mucosal atrophy** Gastritis, autoimmune **Pernicious anemia (see below)** **Post-gastrectomy**	**Malabsorption** Crohn's, celiac disease, pancreatic insufficiency, *H. pylori* **Stagnant bowel** Blind loop, stricture **Fish tapeworm** **Resection of ileum** **Drugs** Neomycin, biguanides, proton pump inhibitors, N_2O anesthesia, metformin	**Transcobalamin II deficiency** **IF receptor defect**

Pathophysiology of Pernicious Anemia

- auto-Abs produced against gastric parietal cells leading to achlorhydria and lack of IF secretion
- IF is required to stabilize B$_{12}$ as it passes through the bowel
- decreased IF leads to decreased ileal absorption of B$_{12}$
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- most common in Northern European White populations, usually >30 yr (median age of 60 yr)

Clinical Features

- neurological (severity of anemia and neurological sequelae depends on deficiency)
  - peripheral neuropathy (variable reversibility)
    - usually symmetrical, affecting lower limbs more than upper limbs
  - spinal cord (irreversible damage)
    - subacute combined degeneration
    - posterior columns: decreased vibration sense, proprioception, 2-point discrimination, and paresthesia
    - pyramidal tracts: spastic weakness, ataxia
  - cerebral (common, reversible with B$_{12}$ therapy)
    - confusion, delirium, and dementia
  - cranial nerves (rare)
    - optic atrophy

Investigations

- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
  - MCV >110 fL
  - low reticulocyte count relative to the degree of anemia (<2%)
- serum B$_{12}$ and RBC folate
  - caution: lower serum B$_{12}$ leads to low RBC folate; absence of B$_{12}$ results in folate polyglutamate synthesis failure
  - alternatively, can measure elevated urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils

- BM
  - hypercellularity due to abnormal proliferation and maturation of multiple myeloid cell lines
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- celiac disease testing
- bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- pernicious anemia investigations: anti-parietal cell Ab (more sensitive), anti-intrinsic factor Ab (more specific), gastrin level (elevated), upper endoscopy (for biopsy - atrophic gastritis, also to screen for gastric malignancy)

Treatment
- treatment dose = vitamin B12 1000-1200 µg PO once daily if intestinal absorption intact or 1000 µg IM weekly; route and duration depends on cause
- maintenance dose (once replete) = vitamin B_{12} 1000 µg PO once daily or 1000 µg IM monthly
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation (enriched in flour)
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables, and fortified cereals
- maternal folate deficiency is associated with fetal neural tube defects

Etiology

Table 17. Etiology of Folate Deficiency

Diet/Deficiency	Malabsorption	Drugs	Increased Demand
Alcohol use disorder	Celiac disease	Anti-folates (methotrexate)	Pregnancy
Substance misuse	IBD	Anticonvulsants (phenytoin)	Hemolysis
Elderly/infants	Short bowel syndrome	Alcohol	Prematurity
Poor intake		Oral contraceptive	Exfoliative dermatitis/psoriasis
			Hemodialysis

Clinical Features
- anemia, mild jaundice, glossitis, diarrhea, confusion, pallor
- consider social history, alcohol use disorder/substance misuse, very poor diet (e.g. elderly, depressed)

Investigations
- similar to B_{12} deficiency (CBC, reticulocytes, blood film, RBC folate, and serum B_{12})
- if decreased RBC folate, rule out B_{12} deficiency as cause

Management
- folic acid 1-5 mg PO once daily x 1-4 mo; then 1 mg PO once daily maintenance if cause is not reversible

Never give folate alone to an individual with megaloblastic anemia because it will mask B_2 deficiency and neurological degeneration will continue

Hemostasis

Stages of Hemostasis

1. Primary Hemostasis
- mediated by platelets and VWF
- goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (*Figure 12a, H27*)
  - adhesion: platelets adhere to subendothelium via VWF
  - activation: platelets are activated resulting in morphology change, and granule release
  - aggregation: activated GPIIbIIIa on platelets binds soluble ligands, which results in aggregation and the formation of a localized platelet plug

2. Secondary Hemostasis
- platelet plug is reinforced by production of a fibrin clot (*Figure 12b, H27*)
- extrinsic (initiation) pathway: initiation of secondary hemostasis
- intrinsic (amplification) pathway: amplification once secondary hemostasis has started via positive feedback
- both the intrinsic and extrinsic pathways converge onto the common pathway, which results in thrombin generation and fibrin formation

3. Fibrin Stabilization
- conversion from a soluble to an insoluble, cross-linked clot

4. Fibrinolysis
- once healing is initiated, clot dissolution is mediated by the fibrinolytic system

Phases of Hemostasis
Primary Hemostasis
Vascular response and platelet plug formation via VWF
Secondary Hemostasis
Fibrin clot formation
Fibrin Stabilization
Fibrinolysis

Check out this educational module created by St. Michael's Hospital residents and hematology faculty: www.coagtesting.com

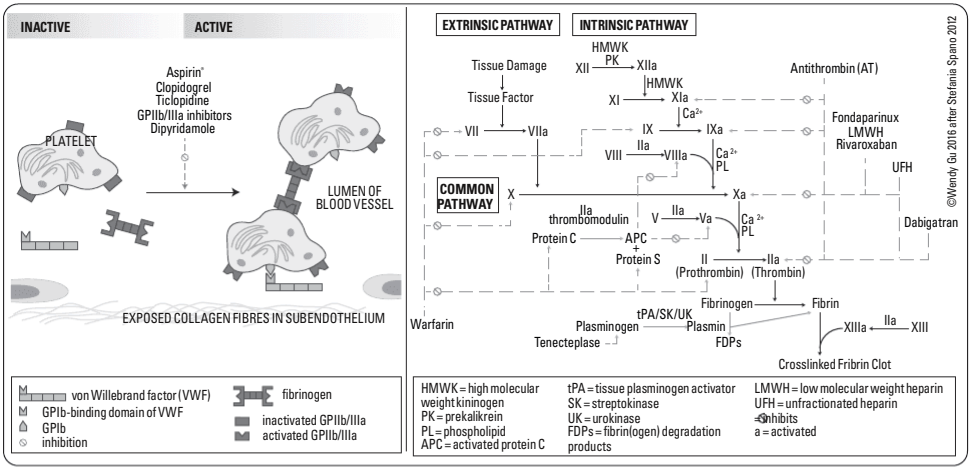

Figure 12a. Platelet activation

Figure 12b. Coagulation cascade

Table 18. Commonly Used Tests of Hemostasis

Type of Hemostasis	Test	Typical Reference Range (lab dependent)	Purpose	Examples of Associated Diagnoses
Primary	Platelet count	150-400 x 10^9/L	To quantitate platelet number	Low in ITP, HUS/TTP, DIC, HIT
Secondary	PTT	28-38 s	Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway Used to monitor heparin and argatroban therapy	Prolonged in hemophilia A and B (if factor deficiency is below reagent threshold of detection) N.B. Prolonged if lupus anticoagulant present (inhibits pathway *in vitro*)
	PT	10-13 s	Measures extrinsic pathway (factor VII) and common pathway	Prolonged in vitamin K deficiency, vitamin K antagonist therapy (warfarin), factor VII deficiency
	INR	0.9-1.2	Used to monitor warfarin therapy and for assessment of hepatic function	
	Mixing studies		May differentiate inhibitors of coagulation factor(s) from a deficiency in coagulation factors Mix patient's plasma with normal plasma in 1:1 ratio and repeat abnormal test	Normalization of coagulation time if deficiency of single coagulation factor (normalization may not occur if multiple coagulation factors are deficient) Lack of normalization if inhibitor present
Fibrinolysis	Euglobulin lysis time	N >90 min	Looks for accelerated fibrinolysis	May be shortened (increased fibrinolysis) in DIC or factor XIII deficiency
Other	Fibrinogen D-dimer Specific factor assays (e.g. factor VIII) Lupus anticoagulant von Willebrand tests (VWF antigen, Ristocetin cofactor activity (VWF activity), factor VIII)			

Note: INR is mathematically derived from PT

Table 19. General Rules of Thumb: Signs and Symptoms of Disorders of Hemostasis

	Primary (Platelet, VWF)	Secondary (Coagulation)
Surface Cuts	Excessive, prolonged bleeding	Normal/slightly prolonged bleeding
Onset After Injury	Immediate	Delayed
Site of Bleeding	Superficial i.e. mucosal (nasal, gingival, GI tract, vaginal), skin	Deep i.e. joints, muscles (excessive, post-traumatic)
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas

Tests of Secondary Hemostasis

PT/INR: Tennis is played outside (Extrinsic pathway)
PTT: Table **T**ennis is played inside (Intrinsic pathway)

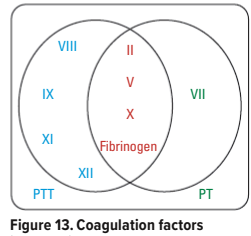

Figure 13. Coagulation factors involved in PT and PTT

Causes of a Prolonged PTT without Bleeding include:
1. Early contact factor (Factor XII, HMWK, PK) deficiency
2. Lupus anticoagulant
3. Inappropriate blood draw
4. Laboratory error

Consider PTT
IV heparin, argatroban monitoring
Factor VIII deficiency (Hemophilia A), Factor IX deficiency (Hemophilia B), factor XI deficiency, severe VWD

Table 20. Lab Values in Disorders of Hemostasis

	PT	PTT	Platelet Count	Hb
Hemophilia A/B	N	↑	N	N*
VWD	N	±	N/↓	N*
DIC	↑	↑	↓	N/↓
Liver Failure	↑	N/↑	N/↓	N
ITP	N	N	↓	N*
TTP	N	N	↓	↓

* = anemia may develop from progressive iron deficiency and/or active bleeding

Consider PT/INR
Warfarin
Liver disease
Risk factor for vitamin K deficiency (e.g. malabsorption, cholestasis, malnutrition)

Consider both PTT and PT/INR
Suspected DIC
Trauma patient, or requiring massive transfusion protocol
Bleeding patient
Patient receiving thrombolytic therapy

Disorders of Primary Hemostasis

Definition

- inability to form an adequate platelet plug due to:
  - disorders of blood vessels
  - disorders of platelets: abnormal function/numbers
  - disorders of VWF
- characterized as immediate bleeding, mucocutaneous bleeding, and manifesting as petechiae/ecchymosis/ epistaxis/ gum bleeding/ menorrhagia

Classification

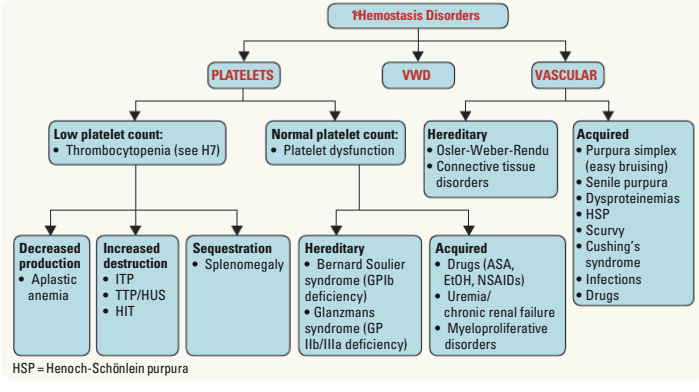

Figure 14. Approach to disorders of primary hemostasis

Drugs Commonly Associated with Thrombocytopenia

Trimethoprim/ sulfamethoxazole	Heparin	NSAIDs
Vancomycin	Digoxin	Acetaminophen
Rifampin	Amiodarone	Ethanol
Ethambutol	Quinidine	H2-antagonists
Amphotericin B	Quinine (common)	Chemotherapy

Immune Thrombocytopenia

Table 21. Features for Childhood vs. Adult Immune Thrombocytopenia

Features	Childhood ITP (see Pediatrics, P53)	Adult ITP
Peak Age	2-6 yr	20-40 yr
Gender	F=M	F>M
History of Recent Infection	Common	Rare
Duration	Usually wk	Mo to yr
Spontaneous Remissions	80% or more	Uncommon

Definition

- a disease of low platelet count (see *Thrombocytopenia, H7*) secondary to aberrant immune responses

Terminology of ITP

- primary: ITP (platelet count <100 x 10^9/L) with no other cause of thrombocytopenia
- secondary: ITP associated with another condition (e.g. HIV, HCV, SLE, or CLL)
- drug-induced: platelet destruction caused by anti-platelet Abs secondary to drug exposure

Classification of Primary ITP

- acute: 3 mo from diagnosis
- persistent: 3-12 mo from diagnosis

- chronic: >12 mo from diagnosis
- refractory: post-splenectomy

Pathophysiology
- primary or secondary ITP
- an acquired immune-mediated disorder
  - increased platelet destruction induced by medications, viral infections, autoimmune diseases, and pregnancy
    - anti-platelet Abs bind to platelet surface → increased splenic clearance
    - helper T-cell and cytotoxic T-cell activation
- impaired platelet production
  - myelosuppression mediated by cytotoxic chemotherapy
  - drug induced megakaryocyte suppression

Clinical Features
- variable presentation: asymptomatic, fatigue, minimal bruising, mucocutaneous bleed (e.g. purpura, ecchymoses, petechiae, continuous epistaxis, menorrhagia) most common but bleeding can occur anywhere including intracranial hemorrhage
- assess for symptoms/signs suggesting a secondary cause

Investigations
- CBC: platelet count <100 x 10^9/L
- PT and PTT: normal
- peripheral blood film: decreased platelets ± large platelets (rule out platelet clumping)
- HIV, HCV
- depending on clinical suspicion: *H. pylori* testing (urea breath test, stool antigen, or endoscopy) vitamin B_{12}, ANA, C3, C4, APLA, quantitative immunoglobulins (to rule out underlying immunodeficiency) depending on clinical symptoms
- blood group RhD typing
- BM aspirate and biopsy: increased number of megakaryocytes
  - BM aspirate and biopsy should be considered pre-splenectomy to confirm diagnosis or if there is suspicion of diminished BM function (systemic symptoms, refractory ITP and/or abnormal blood film)

Treatment
- rarely indicated if platelets >30 x 10^9/L unless active bleeding, trauma, or surgery
- emergency treatment (active bleeding (CNS, GI, or GU) or in need of emergency surgery)
  - general measures: stop antiplatelet medications, control blood pressure, minimize trauma
  - corticosteroids: prednisone (0.5-2 mg/kg/d) or dexamethasone (40 mg PO once daily x 4 d)
  - if corticosteroids contraindicated: IVIg 1 g/kg x 1 dose, to be repeated if necessary (raises platelet count faster than corticosteroids)
  - IVIg can be used with corticosteroids when a more rapid increase in platelet count is required
  - antifibrinolytic: tranexamic acid (1 g PO TID or 1 g IV q8 h) if mucosal bleeding
  - platelet transfusion: for refractory, major bleeding, or need for urgent surgery (expect that platelet recovery will be diminished)
  - management of life threatening bleeding (i.e.intracranial bleeding): IV steroids, IVIg, platelet transfusion, may also consider emergency splenectomy -vaccinations prior if possible (*S. pneumoniae, N. meningitidis*, and *H. influenzae* type b)
  - management of intracranial bleeding: IV steroids, IVIg, platelet transfusion
- non-urgent treatment (platelet count <20-30 x 10^9/L and no bleeding)
  - 1st-line
    - corticosteroids (dexamethasone 40 mg PO once daily x 4 d x 1-4 cycles (not wk) or prednisone (0.5-2 mg/kg/d) x 2-3 wk then slow taper over 6 wk)
    - IVIg 1 g/kg
    - anti-D: appropriate for Rh+ non-splenectomized patients, but can cause transient hemolysis (avoid if low Hb at baseline or if DAT is positive)
  - 2nd-line
    - splenectomy (need vaccinations prior to splenectomy: *S. pneumoniae, N. meningitidis*, and *H. influenzae* type b) – not preferred if within 12 mo from diagnosis
    - thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag) – may not be accessible as second line due to funding considerations
    - rituximab
  - 3rd-line
    - immunomodulating therapy (azathioprine, cyclophosphamide, danazol, and vincristine)
      - may be considered as defacto second line due to funding considerations and access limitations to other treatments
    - Syk inhibitors (Fostamatinib) - blocks platelet clearance

Definitions of Response to Treatment
- complete response: platelet count >100 x 10^9/L
- partial response: platelet count 30-100 x 10^9/L
- no response: platelet count <30 x 10^9/L

Prognosis

- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- life expectancy similar to general population (however, risk of mortality from bleeding/infection increases with advancing age)
- major concern is spontaneous intracranial hemorrhage, more common in the elderly

Table 22. Heparin-Induced Thrombocytopenia (HIT)

Pathophysiology	Immune mediated Ab recognizes a complex of heparin and platelet factor 4 leading to platelet activation via platelet Fc receptor and activation of coagulation system
Diagnosis	Suspected with intermediate or high probability HIT score Screen with immunoassays (e.g. HIT ELISA) and confirm with functional testing (Serotonin Release Assay)
Onset of Decreased Platelets	5-14 d (if previously exposed to heparin within 100 d, HIT can develop in hours due to an anamnestic response)
Risk of Thrombosis	30-50% (25% of events are arterial) if untreated
Clinical Features	Bleeding complications uncommon Venous thrombosis: DVT, PE, limb gangrene, cerebral venous sinus thrombosis Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney) Heparin-induced skin necrosis (with LMWH) Non-necrotizing erythematous skin lesions Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.)
Specific Tests	Pre-test clinical scoring models can help rule-out HIT: 4Ts and the HIT Expert Probability (HEP) score 14C serotonin release assay (tests the functional ability of patient's plasma to activate platelets) ELISA for HIT-Ig (more sensitive, less specific than serotonin assay, faster turnaround time, high negative predictive value) Ultrasound of lower limb veins and upper extremity with central venous catheter for DVT
Management	Clinical suspicion of HIT should prompt discontinuation of UFH and LMWH including flushes (specific tests take several days) Initiate anticoagulation with a non-heparin anticoagulant: e.g. argatroban, danaparoid, fondaparinux, bivalirudin unless there is a strong contraindication (duration depends on presence or absence of thrombosis) warfarin should be started when platelet count >150 x 10^9/L DOACs can be started before platelet count recovery Allergy band and alert in patient records

Table 23. The 4T Pre-Test Clinical Scoring Model for HIT

Category	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall >50% AND platelet nadir ≥20 x 10^9/L	Platelet count fall 30-50% OR platelet nadir 10-19 x 10^9/L	Platelet count fall <30% OR platelet nadir <10 x 10^9/L
Timing of Platelet Count Fall	Clear onset between 5-10 d of heparin exposure OR platelet count fall at ≤1 d if prior heparin exposure within last 30 d	Consistent with fall in platelet count at 5-10 d but unclear (e.g. missing platelet counts) OR onset after 10 d OR fall ≤1 d with prior heparin exposure within 30-100 d	Platelet count fall after ≤4 d of heparin exposure, and no recent heparin
Thrombosis or Other Sequelae	Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus, adrenal hemorrhage	Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven	None
Other Causes for Thrombocytopenia	None apparent	Possible	Definite

6-8 points = high probability of HIT; 4-5 points = intermediate probability of HIT; 0-3 points = low probability of HIT

Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360-3392

Heparin-induced thrombocytopenia (previously known as HIT type II): immune-mediated reaction following treatment with heparin leading to platelet activation and subsequent coagulation activation
Heparin-associated thrombocytopenia (previously known as HIT type I): transient thrombocytopenia following administration of heparin

Heparin-Associated Thrombocytopenia (previously known as HIT type I)

- Direct heparin mediated platelet aggregation (non-immune)
- Platelets >100 X 10^9/L
- Self-limited (no thrombotic risk)
- May continue with heparin therapy
- Onset 24-72 h

LMWH is also associated with HIT, but the risk is less than unfractionated heparin (2.6% in UFH vs. 0.2% in LMWH)

American Society of Hematology Choosing Wisely Recommendation
Don't test or treat for HIT in patients with low pre-test probability of HIT (4T's score of 0-3) as HIT can be excluded
Do not discontinue heparin or start a non-heparin anticoagulant in these low-risk patients because of increased risk of bleeding and increased cost of alternatives

Thrombotic Microangiopathies (TMAs)

Definition

- thrombotic disorder characterized by thrombi formation in small blood vessels
- TTP, HUS, and aHUS are examples of TMAs

Table 24. TTP and HUS

	TTP	HUS (see Pediatrics, P82)
Epidemiology	Immune form presents predominantly in adults Congenital form presents predominantly in children	Predominantly children and elderly
Etiology	Deficiency of ADAMTS13: metalloproteinase that breaks down ultra-large VWF multimers Congenital (genetic absence of ADAMTS13) Acquired (drugs, malignancy, transplant, HIV-associated, and idiopathic)	Shiga toxin (*E. coli* serotype 0157:H7) in 90% Other bacteria, viruses, genetic causes, and drugs
Clinical Features	1. Thrombocytopenia 2. MAHA/TMA 3. Neurological symptoms: headache, confusion, focal defects, and seizures 4. Symptoms can be mild and non-specific	1. Severe thrombocytopenia 2. MAHA/TMA 3. Acute kidney injury 4. Bloody diarrhea 5. GI prodrome
Investigations (both TTP, HUS)	CBC and blood film: decreased platelets and increased schistocytes PT, PTT, fibrinogen: normal Markers of hemolysis: increased unconjugated bilirubin, increased LDH, and decreased haptoglobin Negative Coombs test/DAT Creatinine and urea to follow renal function (kidney injury is uncommon in TTP vs. HUS induces severe injury that is sudden in onset) ADAMTS13 gene, activity or inhibitor testing (TTP)	
Management	Medical emergency: TTP mortality ~90% if untreated Plasma exchange ± steroids Platelet transfusion avoided unless life-threatening bleed (associated with microvascular thrombosis) Plasma infusion if plasmapheresis is not immediately available Caplacizumab in certain cases of acquired TTP	Supportive therapy (fluids, RBC transfusion, nutrition, etc.) Some evidence for plasma exchange Possible role of eculizumab (C5 Ab blocks complement activation) for neurologic symptoms

Note: aHUS is a complex disease with different etiology, treatment depends on genetic abnormalities

Pathophysiology of TTP

- Normally, large VWF multimers secreted by endothelial cells are rapidly cleaved by ADAMTS13 protease
- Congenital TTP is due to a genetic deficiency in ADAMTS13
- Acquired TTP (the more common form) is due to Abs against ADAMTS13
- Without ADAMTS13, uncleaved VWF continues to promote platelet adhesion, causing excess platelet aggregation in small blood vessels

Differential Diagnosis of TTP

DIC
HUS
aHUS
HELLP
Catastrophic APS
Evans syndrome (AIHA + ITP)

von Willebrand Disease

Definition

- bleeding disorder characterized by impaired clot formation due to qualitative or quantitative deficiencies in VWF

Pathophysiology

- most common inherited bleeding disorder (prevalence of 1%)
- usually autosomal dominant (types 2N and 3 are autosomal recessive)
- women more commonly diagnosed (heavy menstrual bleeding, peripartum bleeding)
- qualitative defect or quantitative deficiency of VWF depending on type
  - VWF mediates platelet adhesion/aggregation and acts as a chaperone for Factor VIII (extending its half-life in circulation); abnormal VWF can affect both primary and secondary hemostasis
  - VWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion/aggregation
    - both large and small multimers complex with Factor VIII
    - VWF levels vary according to blood group (lowest in group O patients) and other factors (higher with pregnancy, hormonal medication, acute inflammation)

Classification

- type 1: mild quantitative deficiency (decreased amount of VWF and proportional decrease in VWF activity) – 80% of cases
- type 2: qualitative defect (VWF activity disproportionally lower than quantity) – 20% of cases
  - type 2A: reduced VWF-dependent platelet adhesion due to high and intermediate molecular weight VWF multimer deficiency
  - type 2B: increased affinity for platelet GPIb and subsequent loss of high and intermediate molecular weight VWF multimers
  - type 2M: reduced VWF-dependent platelet adhesion with normal VWF multimer levels
  - type 2N: decreased affinity for Factor VIII
- type 3: severe total quantitative defect (virtually no VWF produced) – 1 in 1000000

Clinical Features

- bleeding history is the single most important predictor of an underlying bleeding disorder
- validated, standardized bleeding assessment tools (e.g. ISTH-BAT) to facilitate exploration of the bleeding history
- mucocutaneous bleeding (easy bruising, epistaxis (>10 min), heavy menstrual bleeding, peripartum bleeding, post-dental extraction bleeding, excessive postoperative bleeding, and unexplained gastrointestinal bleeding)

  - type 3 VWD patients can experience musculoskeletal bleeding due to significant deficiency in Factor VIII (lack of Factor VIII chaperoning as VWF is absent)
- family history of a bleeding disorder (a negative family history cannot be used to exclude the diagnosis)

Investigations
- CBC, platelet, VWF antigen (determine how much VWF is present), VWF ristocetin cofactor activity (determine how well VWF binds to platelet), Factor VIII (determine how well VWF chaperones Factor VIII), and PTT
- tests to further categorize type/subtype of VWD: multimer analysis, ristocetin induced platelet agglutination, and genetic studies

Table 25. Investigations in VWD

Test	Expected Result
PTT	N/↑
Plt Count	N/↓ (can be low in type 2B)
Blood group	Affects antigen quantification (↓ in group O)
Ferritin	Rule out secondary iron deficiency due to bleeding
von Willebrand antigen	↓
Ristocetin activity	↓ (cofactor for VWF-Plt binding)
Factor VIII	N/↓
VWF multimer analysis	Multimer variants

Consider VWD in all women with heavy menstrual bleeding

VWD is the most common heritable bleeding disorder

Treatment
- DDAVP® is effective treatment for 85-90% of patients with type 1 VWD and for some subtypes of type 2 VWD
  - causes release of VWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs after 4 consecutive doses
  - need to document responsiveness with "DDAVP® challenge"
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
- VWF:Factor VIII concentrate (Humate P®, Wilate®) if DDAVP® unresponsive/clinically ineffective or for severe bleeding episode
  - need to monitor VWF and factor VIII levels (very high factor VIII level can be prothrombotic)
- gynecologic focused care for heavy menstrual bleeding (N.B. estrogens have the added benefit of increasing VWF levels)

Prognosis
- patients with mild type 1 VWD usually have auto-correction of VWF deficiency in pregnancy
- most cases are mild-moderate, and only ~10% of cases require long-term prophylactic therapy

Disorders of Secondary Hemostasis/Fibrinolysis

Definition
- inability to form an adequate fibrin clot
  - disorders of coagulation factors or cofactors
  - disorders of proteins associated with fibrinolysis
- patients can experience bleeding anywhere in the body but delayed bleeding, deep muscular bleeding, and spontaneous hemarthroses are highly suggestive of disorders of secondary hemostasis/fibrinolysis

Table 26. Classification of Secondary Hemostasis Disorders

Hereditary	Acquired
Factor VIII deficiency: Hemophilia A, VWD	Liver disease
Factor IX deficiency: Hemophilia B (Christmas Disease)	DIC
Factor XI deficiency: Hemophilia C	Vitamin K deficiency
Other factor deficiencies are rare	Acquired inhibitors (Factor VIII most common)

Hemophilia A (Factor VIII Deficiency)

Pathophysiology
- X-linked recessive disorder where factor VIII is absent or deficient, 1 in 5000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

Clinical Features
see *Table 19, H27* under secondary coagulation
- patients may have also acquired HIV or HCV from contaminated blood products (no cases observed from transfusions in Canada since 1985)

Investigations
- CBC
- prolonged PTT, normal INR (PT)
- decreased factor VIII (<40% of normal)
- VWF antigen and ristocetin activity testing to rule out VWD

Treatment
- DDAVP® in mild hemophilia A
- factor VIII concentrate for:
  - prophylaxis (recommended for patients with severe hemophilia A)
  - on-demand (i.e. to treat a bleed)
- antifibrinolytic agents (e.g. tranexamic acid), especially for mucosal bleeds

Hemophilia B (Factor IX Deficiency)

- X-linked recessive, 1 in 30000 males; approximately half have severe disease (factor IX activity <1% of normal)
- clinical and laboratory features identical to hemophilia A (except deficiency in factor IX instead of factor VIII)
- treatment: factor IX concentrate (prophylaxis or on-demand), antifibrinolytic agents

Factor XI Deficiency

- autosomal recessive; more common in Ashkenazi Jewish population
- usually mild (severe spontaneous bleeding is rare), often diagnosed in adulthood following bleeding challenge (e.g. surgery)
- factor XI level does not correlate proportionally with bleeding risk – risk of bleeding correlates with a previous history or family history of bleeding
- treatment: antifibrinolytic agents, FP, Factor XI concentrate, DDAVP®

Liver Disease

- see Gastroenterology, G32

Pathophysiology
- thrombocytopenia secondary to: hypersplenism, nutritional deficiency, direct BM toxicity related to alcohol, diminished production from chronic viral infections (e.g. HCV), and decreased production of TPO
- deficiency in synthesis of all factors except VIII (also made in endothelium)
- aberrant or diminished synthesis of fibrinogen (factor I)
- diminished synthesis of natural anticoagulants and altered regulation of fibrinolysis

Investigations
- CBC, peripheral blood film: thrombocytopenia, target cells
- primary hemostasis affected
  - thrombocytopenia
- secondary hemostasis affected
  - elevated INR (PT), PTT, TT
  - low fibrinogen in end-stage liver disease

Investigations in Liver Disease
Factor V, VII, VIII. Expect decreased V and VII because they have the shortest half-life. Factor VIII will be normal or increased because it is produced in the endothelium

Treatment
- supportive, treat liver disease, blood products if active bleeding (FP, platelets, cryoprecipitate)

Vitamin K Deficiency

Etiology
- drugs
  - vitamin K antagonist (e.g. warfarin) – diminished production of functional Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet: e.g. prolonged fasting or starvation (especially due to chronic alcohol consumption)
- biliary obstruction
- chronic liver disease (decreased stores)
- fat malabsorption (e.g. celiac disease, disorders of bile or pancreatic secretion, intestinal disease, and cystic fibrosis)

Vitamin K Dependent Factors
Vitamin K antagonists (e.g. warfarin) affect function of these factors:
"**1972** **C**anada vs. **S**oviets"
X, IX, VII, II, proteins **C** and **S**

PT should improve within 24 h of adequately dosed vitamin K repletion (onset is in 6-12 h); if not, search for other causes

Investigations
- INR (PT) is elevated out of proportion to elevation of the PTT
- decreased Factors II, VII, IX, X (vitamin K-dependent)

Treatment
- hold anticoagulant if vitamin K antagonist on board
- vitamin K PO if no active bleeding
- if bleeding, give vitamin K 10 mg IV (reversal may take up to 12 h)
- if life-threatening bleeding and vitamin K antagonist used, give PCC or FP if PCC contraindicated
  - PCCs are relatively contraindicated in liver disease or if there is a previous history of HIT (PCC product contains heparin)

American Society of Hematology Choosing Wisely Recommendation
Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (e.g. outside of the setting of major bleeding, intracranial hemorrhage, or anticipated emergent surgery)

Disseminated Intravascular Coagulation

Definition
- excessive, dysregulated release of plasmin and thrombin leading to intravascular coagulation and fibrinolysis
- depletion of platelets, coagulation factors, and fibrinogen
- risk of life-threatening hemorrhage and/or thrombosis

Etiology
- occurs as a complication of many other severe medical, surgical, or obstetrical conditions
- widespread endothelial damage and extensive inflammatory cytokine release

DIC is a spectrum which may include thrombosis, bleeding, or both

Clinical Features
- presence of both hemorrhage and clotting

Table 27. Clinical Features of DIC

Signs of Microvascular Thrombosis	Signs of Hemorrhagic Diathesis
Neurological: multifocal infarcts, delirium, coma, seizures **Skin:** focal ischemia, superficial gangrene, purpura fulminans **Renal:** oliguria, azotemia, cortical necrosis **Pulmonary:** ARDS **GI:** acute ulceration, liver dysfunction **Adrenal failure:** adrenal hemorrhage or infarction **RBC:** microangiopathic hemolysis (schistocytes)	**General:** Bleeding from any site in the body (secondary to decreased platelets and coagulation factors) **Neurologic:** intracranial bleeding **Skin:** petechiae, ecchymosis, oozing from puncture sites **Renal:** hematuria **Mucosal:** gingival oozing, epistaxis, massive bleeding

Factor Levels in Acquired Coagulopathies

Factor	Liver Disease	Vitamin K Def	DIC
V	↓	N	↓
VII	↓	↓	↓
VIII	N/↑	N	↓

Important Etiologies of DIC

OMITS
Obstetric complications
Malignancy
Infection
Trauma
Shock

Investigations
- peripheral blood smear: schistocytes
- primary hemostasis: CBC, decreased platelets
- secondary hemostasis: prolonged INR (PT), PTT, TT, decreased fibrinogen and other factors
- accelerated fibrinolysis: increased FDPs or D-dimers and short euglobulin lysis time

Treatment
- individualize supportive therapy according to underlying condition: recognize early and treat underlying disorder – supportive measures: hemodynamic and/or ventilator support, aggressive hydration, and RBC transfusion if severe bleed
- in bleeding phase (recommendations from ISTH Guidance Statement 2013):
  - treat the underlying condition
  - transfuse platelets in patients with active bleeding if platelet count <50 x 10^9/L or in those with a high-risk of bleeding and a platelet count of <20 x 10^9/L
  - FP may be useful in patients with active bleeding with either prolonged PT/aPTT (>1.5 times normal). FP should be considered in DIC patients requiring an invasive procedure with similar laboratory abnormalities
  - fibrinogen concentrate or cryoprecipitate may be recommended in actively bleeding patients with persisting severe hypofibrinogenemia (<1.5 g/L)
  - PCC may be considered in actively bleeding patients if FP transfusion is not possible
- in thrombotic phase:
  - LMWH preferred over UFH in critically ill, non-bleeding patients

Clinical Prediction of DIC - International Society of Thrombosis and Hemostasis (ISTH) Calculator
Presence of an underlying, predisposing condition is a requirement

DIC diagnosis is defined as ≥5 points

Points	0	1	2	3
Platelet count x 10^9/L	>100	50-100	<50	
Level of Fibrin markers (D-dimer or FDP)	No increase		Moderate increase <5 x ULN	Strong increase ≥5 x ULN
Prolonged PT (s)	<3	≥3-6	≥6	
Fibrinogen (g/L)	>1.0	≤1.0		

Table 28. Differential Diagnosis for Abnormal Coagulation Testing

Increased PT/INR Only	Increased PTT Only	Both Increased
Warfarin Vitamin K deficiency Factor VII deficiency Liver disease Factor VII inhibitors	Intrinsic factor deficiency: Factor VIII (Hemophilia A), Factor IX (Hemophilia B), Factor XI, Factor XII Heparin, DOACs Antiphospholipid Ab Intrinsic factor inhibitors (e.g. Factor VIII)	Deficiency of common pathway factors: Prothrombin (Factor II), fibrinogen, Factor V, Factor X Severe liver disease Factor V, Factor X, prothrombin, and fibrinogen inhibitors Excessive anticoagulation Severe vitamin K deficiency

Hypercoagulable Disorders

Hypercoagulability Workup – Venous Thrombosis

- workup for hypercoagulable state should be considered *ONLY* if it will alter treatment decisions
- includes inherited or acquired thrombophilia
  - hypercoagulability workup may be considered in patients with:
    - multiple recurrent thromboses
    - warfarin-induced skin necrosis or neonatal purpura fulminans (protein C or S deficiency)
    - thrombosis at an unusual venous site
    - abnormal blood work, constitutional symptoms, or physical exam findings suggestive of cancer
  - arterial thrombotic events due to a hypercoagulable state are typically associated with APS, HIT, JAK2+ MPNs, and PNH, not hereditary thrombophilias
- workup (if indicated)
  - initial
    - CBC, blood smear, coagulation studies, liver/renal function tests, urinalysis, and hemolysis markers (if anemic)
    - malignancy history, age appropriate cancer screening
    - serology: APLA (lupus anticoagulant will be affected by anticoagulation)
    - depending on CBC, consider JAK2
  - post-treatment (or ≥6 wk, as protein levels are depleted/consumed by clot and can be affected by anticoagulation)
    - antithrombin activity
    - proteins C, S activity
- note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state
- decision to pursue hypercoagulability workup should be made in consultation with a hematologist

SELECTED CAUSES OF HYPERCOAGULABILITY

Factor V Leiden (Activated Protein C Resistance)

- most common cause of hereditary thrombophilia
- 3-7% of European White population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

Prothrombin Gene Mutation (PT) G20210A

- 1-3% of European White population are heterozygotes
- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Protein C and Protein S Deficiency

- protein C inactivates Factors Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous or compound heterozygous: neonatal purpura fulminans
  - heterozygous
    - type I: decreased protein C levels
    - type II: decreased protein C activity
  - acquired: liver disease, sepsis, DIC, warfarin, and certain chemotherapeutic agents
  - 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, and warfarin

Antithrombin Deficiency

- antithrombin slowly inactivates thrombin, a process accelerated by heparin
- causes/etiology: autosomal dominant inheritance, urinary losses in nephrotic syndrome, or reduced synthesis in liver disease
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to UFH (LMWH may be considered, with monitoring of anti-Xa levels)
  - heparin resistance: suspect if >35000 IU of UFH required during 24 h use

Elevated Factor VIII Levels

- an independent marker of increased incident and recurrent thrombotic risk, but levels can also be increased in numerous states as an acute phase reactant, therefore its clinical use is controversial

Differential Diagnosis of Elevated D-Dimer

- Arterial thromboembolic disease (e.g. MI, cerebrovascular accident, acute limb ischemia, AFib, intracardiac thrombus)
- Venous thromboembolic disease (e.g. DVT, PE)
- Abnormal fibrinolysis (e.g. use of thrombolytic agents)
- Surgery/trauma (e.g. tissue ischemia, necrosis)
- Vaso-occlusive episode of SCD
- Renal disease (nephrotic syndrome, acute/chronic renal failure)
- Pregnancy-related (e.g. normal pregnancy, preeclampsia, eclampsia)
- Cardiovascular-related (e.g. cardiovascular disease, CHF)
- Severe infection/sepsis/inflammation, systemic inflammatory response syndrome
- DIC
- Malignancy
- Severe liver disease
- Venous malformation

Isolated prolonged INR is most commonly due to Factor VII deficiency in the extrinsic pathway since it has the shortest half-life
Isolated elevated PTT is usually due to factor deficiency or inhibitors in the intrinsic pathway

American Society of Hematology Choosing Wisely Recommendations

1. Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (i.e. surgery, trauma, or prolonged immobility)
2. Do not use inferior vena cava filters routinely in patients with acute venous thromboembolism

Common Causes of Hypercoagulability

CALM APES
Protein **C** deficiency
APS
Factor **V** Leiden
Malignancy
Antithrombin deficiency
Prothrombin G20210A
Increased Factor **VIII** (**E**ight)
Protein **S** deficiency

Causes of Both Venous and Arterial Thrombosis include:
APS
MPN
HIT
Distal venous clot with patent foramen ovale
PNH

Protein C, protein S, and ATIII are decreased during acute thrombosis – therefore to test for deficiency, they must be tested outside of this time period

Congenital Dysfibrinogenemia
- may predispose to thromboembolic disease, bleeding, or both

Disorders of Fibrinolysis
- includes congenital plasminogen deficiency, and tPA deficiency, but association with VTE risk is not clear

Antiphospholipid Antibody Syndrome
- definition: ≥1 clinical and ≥1 laboratory criteria
  - clinical: arterial or venous thrombosis, recurrent (>3) early pregnancy losses <10 wk, one late fetal loss ≥10 wk (morphologically normal), or premature birth before 34 wk due to (pre)eclampsia or placental insufficiency
  - laboratory (must be confirmed on two occasions, tested ≥12 wk apart): anticardiolipin IgG and IgM, anti-β2 glycoprotein-I Ab, or lupus anticoagulant
- mechanism: not well understood, Abs interact with platelet membrane phospholipids causing increased activation; can also interfere with thrombin regulation, fibrinolysis, and inhibit the protein C pathway
- see Rheumatology, RH13

Venous Thromboembolism

Definition
- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- includes superficial vein thrombosis , DVT, and PE
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- DVT is more common in lower extremity than upper extremity (upper extremity DVT are increasing due to more central venous access lines)
- incidence ~1% if age >60 yr
- most important sequelae of DVT are PE (~50% chance with proximal DVT) and post thrombotic syndrome (chronic venous insufficiency)
- acutely, PE can result in cardiorespiratory failure and death (rare in treated patients). Most severe chronic sequela of PE is chronic thromboembolic pulmonary hypertension (CTEPH)

Etiology (Virchow's Triad)
- endothelial damage
  - exposure of procoagulant proteins on dysfunctional endothelium promotes thrombosis
  - decreased inhibition of coagulation and local fibrinolysis
  - changes to vessel wall integrity may result in turbulent blood flow
- venous stasis
  - immobilization (e.g. post-MI, CHF, stroke, and postoperative) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see *Hypercoagulable Disorders, H35*)
  - acquired
  - age (risk increases with age)
  - surgery (especially orthopedic, thoracic, GI, and GU)
  - trauma (especially fractures of spine, pelvis, femur, or tibia, and spinal cord injury)
  - neoplasms (especially pancreas, stomach, lung, lymphoma, bladder, testicular, colorectal, and gynecologic - based on the Khorana score)
  - blood dyscrasias (MPNs, especially PV, ET), PNH, hyperviscosity (multiple myeloma, polycythemia, leukemia, and SCD), hemolytic anemias
  - prolonged immobilization (e.g. CHF, stroke, MI, and leg injury)
  - hormone related (combined OCP, hormone replacement therapy, and selective estrogen receptor modulators)
  - pregnancy
  - APS
  - heart failure (risk of DVT greatest with right heart failure and peripheral edema)
    - New York Heart Association (NYHA) Class III and IV
- idiopathic (10-20% are later found to have cancer)

Clinical Features of DVT
- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth, and tenderness; purple-blue colour may indicate severe limb-threatening thrombus
- palpable cord (i.e. thrombosed vein)
- phlegmasia alba dolens (white appearance) and phlegmasia cerula dolens (acute pain and edema) with massive thrombosis
- Homan's sign (pain or resistance with foot dorsiflexion) is unreliable

Differential Diagnosis of DVT
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, and arterial occlusive disease

Malignancy is a Common Cause of Acquired Hypercoagulability

Workup should include:
Complete history and physical
Age appropriate screening:
Mammogram, Pap, PSA, colonoscopy
Additional imaging/laboratory testing based on clinical suspicion
Close follow-up

Screening for Occult Cancer in Unprovoked VTE (SOME)
NEJM 2015;373:697-704
Purpose: To assess the efficacy of a screening program for occult cancer that employs CT of the abdomen and pelvis in patients experiencing their first unprovoked episode of VTE.
Methods: Patients (n=854) were randomly assigned to limited occult-cancer screening or limited occult-cancer screening plus CT.
Results: 3.2% of patients in the limited-screening group and 4.5% of patients in the limited-screening plus CT group received a new diagnosis of occult cancer between the randomization point and 1-year followup (P=0.28). Four occult cancers were missed by the limited screening strategy, while five occult cancers were missed by the limited screening plus CT strategy (P=1.0).
Conclusion: Routine screening with CT in patients who had a first unprovoked VTE did not provide a clinically significant benefit.

Although lupus anticoagulant prolongs PTT, this is a misnomer, as its main clinical feature is thrombosis

Risk of VTE in Hospitalized Patients Receiving Ineffective Antithrombotic Therapy

Risk Factor	RR (95% CI)	P-value
Age >75 yr	1.79 (1.18-2.71)	0.007
Cancer	1.58 (1.01-2.51)	
Previous VTE	1.67 (1.01-2.77)	0.08
Obesity	0.94 (0.59-1.51)	0.91
Hormone therapy	0.51 (0.08-3.38)	0.70
Heart failure	1.08 (0.72-1.62)	0.82
NYHA III	0.89 (0.55-1.43)	0.72
NYHA IV	1.48 (0.84-2.6)	0.27
Acute infectious disease	1.50 (1.00-2.26)	0.06
Acute rheumatic disease	1.45 (0.84-2.50)	0.27

Source: JAMA 2004;164:963-968

Virchow's Triad
Endothelial damage
Blood stasis
Hypercoagulability

Investigations for DVT
- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease (Modified Wells' Pre-test Probability ≤1) and no other acute medical issues; positive result may be non-specific
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
  - sensitivity for calf DVT ~70%
- venography is the gold standard, but is expensive, invasive, and higher risk
- CT pulmonary angiogram or V/Q scan if PE suspected

Post-Thrombotic Syndrome
- development of chronic venous stasis signs and symptoms secondary to a deep venous thrombosis
- symptoms: pain, venous dilatation, edema, pigmentation, skin changes, and venous ulcers
- clinical severity can be assessed using the Villalta score
- large impact on quality of life following a DVT
- treatment: extremity elevation, exercise, compression stockings, and skin/ulcer care
- for clinical features and treatment of PE, see Respirology, R20

Approach to Treatment of Venous Thromboembolism

Purpose
- prevent further clot extension (minimum 3 mo duration)
- prevent acute PE (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- treatment of massive iliofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications (e.g. post-thrombotic syndrome, chronic venous insufficiency, and chronic thromboembolic pulmonary HTN)

Initial Treatment
- consider empiric treatment in patient with moderate/high suspicion of DVT and low-risk of bleeding, if diagnostic imaging will be delayed (definitive imaging should be obtained at first opportunity)
- DOACs
  - apixaban or rivaroxaban alone (with loading dose)
  - dabigatran or edoxaban require 5-10 d of parenteral anticoagulation (usually LMWH) prior to initiation
  - contraindications: during conception/pregnancy, and in breastfeeding women
  - there remains limited evidence in severe renal deficiency and some clinicians do not use DOACs in this population
- LMWH
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule, lab monitoring not required, <1% HIT, safe and effective outpatient therapy (including pregnant and cancer patients)
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis
  - renally cleared – may require dose adjustment in patients with renal dysfunction
- UFH
  - in patients with high-risk of bleed, or requiring rapid interruption for surgical procedures; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT or heparin levels with adjustment of dose to reach therapeutic level (~2x normal value); higher risk for development of HIT

Long-Term Oral Treatment
- anticoagulation therapy
  - warfarin
    - should be initiated with heparin overlap: dual therapy for at least 48 h with INR >2, due to initial prothrombotic state (secondary to warfarin's inhibition of natural anticoagulants protein C/S), half-life of vitamin K factors and risk of warfarin-induced skin necrosis
    - dosed to maintain INR at 2-3, monitor twice weekly for 1-2 wk
    - discontinue heparin after INR >2.0 for 2 consecutive days
  - DOACs
    - apixaban or rivaroxaban: INR not used, patients with CrCl >15 mL/min
    - dabigatran (factor IIa inhibitor) or edoxaban: LMWH or IV heparin for at least 5 d before initiating dabigatran, INR not used, patients with CrCl >15 mL/min (Edoxaban) and >30 mL/min (Dabigatran)
    - important drug interactions to consider for DOACs: inducers or inhibitors of CYP3A4 or P-gp
    - cancer patients: LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients; DOACs are as effective as LMWH (more bleeding observed for patients with GI cancer taking rivaroxaban or edoxaban)

Wells' Score for Predicting DVT
- Paralysis, paresis, or recent orthopedic casting of lower extremity (1)
- Recently bedridden (>3 d) or major surgery within past 4 wk (1)
- Localized tenderness in deep vein system (1)
- Swelling of entire leg (1)
- Calf swelling >3 cm compared to the other leg (measured 10 cm below the tibial tuberosity) (1)
- Pitting edema greater in the symptomatic leg (1)
- Collateral non-varicose superficial veins (1)
- Active cancer or cancer treated within 6 mo (1)
- Alternative diagnosis more likely than DVT (e.g. Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis) (-2)

Total Score Interpretation
3-8: High probability, 1-2: Moderate probability, -2-0: Low probability

Modified Wells' Score
Same as above except with 1 additional point for a history of DVT or major surgery within past 12 wk, and the score interpretation is DVT likely for ≥2 points and DVT unlikely for ≤1 point. D-dimer is ordered for DVT unlikely patients to fully rule out DVT which can help reduce unnecessary ultrasounds

See Landmark Hematology Trials for more information on the CLOT trial. It details the efficacy of low-molecular-weight heparin vs. oral anticoagulant agents in preventing recurrent thrombosis in patients with cancer.

Duration of Treatment with Vitamin K Antagonists (VKA) in Symptomatic Venous Thromboembolism
Cochrane DB Syst Rev 2014;CD001367
Purpose: To evaluate the efficacy and safety of various durations of therapy with VKA in patients with symptomatic VTE.
Study Selection: RCTs comparing various durations of therapy with VKA in patients with symptomatic VTE.
Results: 11 studies (total 3716 participants) were included. A significant reduction in the risk of recurrent VTE was observed during prolonged VKA treatment (RR 0.20, 95% CI, 0.11 to 0.38) independent of the time elapsed since the index thrombotic event. Patients receiving prolonged treatment were at increased risk of bleeding complications (RR 2.60, 95% CI 1.51 to 4.49).
Conclusion: Treatment with VKA strongly reduces the risk of recurrent VTE for as long as they are used. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time).

Common Medications that Interact with Warfarin
Acetaminophen (interference with vitamin K metabolism)
Allopurinol
NSAIDs (GI injury)
Fluconazole
Metronidazole
Sulfamethoxazole
Tamoxifen

- LMWH
  - typically reserved as long term therapy for patients unable to tolerate oral anticoagulants (e.g. unable to absorb oral medications, high risk bleeding patients with intraluminal GI malignancy)
- duration of anticoagulant treatment
  - provoked VTE with transient risk factor: 3 mo
  - provoked VTE with ongoing risk factor: consider indefinite therapy with annual reassessment
  - first unprovoked proximal DVT or PE: ≥3 mo, consider indefinite therapy with annual reassessment
  - second unprovoked VTE: consider indefinite therapy if not already on
  - cancer-associated DVT: consider indefinite therapy for as long as patient has active malignancy (in patients who have cancer in remission, anticoagulation is usually extended for 3-6 mo post last treatment)
  - inferior vena cava filters
  - temporary filter indicated only if acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding) or if anticoagulation must be interrupted (i.e. for urgent surgery)
  - must be retrieved once safe to do so as filter is pro-thrombotic in the long-term and associated with other complications (migration of filter, etc.)
- special considerations
  - pregnancy: treat with LMWH during pregnancy, then LMWH or warfarin for 6 wk post-partum (minimum total anticoagulation time of 3-6 mo, but must include 6 wk post-partum, as this is a high-risk period)
  - avoid warfarin in pregnancy due to teratogenicity outside of select patient populations (e.g. may be used by some thrombosis experts during the second and third trimesters in women with mechanical heart valves)
  - avoid DOAC in conception and pregnancy (due to lack of data) and if breastfeeding in postpartum period
  - surgery: avoid elective surgery in the first 3 mo after a venous thromboembolic event
    - preoperatively: IV heparin may be used up to 4-6 h preoperatively
    - warfarin or DOACs discontinued for at least 2-5 d preoperatively (consider mechanism of drug clearance)
    - postoperatively: IV heparin, LMWH, DOAC can be used for anticoagulation (consult with surgeon prior to re-initiation)
    - for patients at high-risk for thromboembolism (VTE <12 wk, recurrent VTE, APS, AFib with prior stroke, and mechanical heart valve), IV heparin or LMWH (bridging) may be considered before and after the procedure while the INR is below 2.0. Bridging not required for DOACs

In Hospital Prophylaxis

- consider for those with a moderate to high-risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), and intermittent pneumatic compression (IPC)
- LMWH as per hospital protocol (e.g. enoxaparin 40 mg SC once daily, dalteparin 5000 U SC once daily), or rarely UFH 5000 IU SC BID, UFH 5000 IU SC TID
- DOACs for orthopedic surgery thromboprophylaxis

Table 29. Contraindications of Anticoagulant Therapy

Absolute Contraindications to Treatment	Relative Contraindications to Treatment
Active bleeding Severe bleeding diathesis or platelet count <20 x 10^9/L (<20000/mm^3)	Mild-moderate bleeding diathesis or thrombocytopenia Recent major trauma Recent stroke Major abdominal surgery within past 2 d GI/GU bleeding within 1-4 d Endocarditis Neurosurgery or ocular surgery within 10 d

Treatment of Pulmonary Embolism

- see Respirology, R20

Effect of Treatment Delay on the Effectiveness and Safety of Antifibrinolytics in Acute Severe Hemorrhage: a Meta-analysis of Individual Patient-level Data from 40138 Bleeding Patients
Lancet 2018;391:125-132
Purpose: To examine if the effectiveness of antifibrinolytics in reducing death from acute severe hemorrhage is influenced by treatment delay.
Methods: Meta-analysis of individual patient-level data from 2 RCTs with 40138 total patients that investigated the use of tranexamic acid in acute severe bleeding. Treatment benefit was measured by absence of death from bleeding and logistic regression was used to assess the effect of treatment delay.
Results: Overall survival from bleeding was significantly increased by tranexamic acid (OR 1.2; 95% CI 1.08-1.33; P=0.001). Survival was improved by >70% with immediate treatment (OR 1.72, 95% CI 1.42–2.10; P<0.0001). In contrast, treatment benefit was significantly reduced by treatment delay (P<0.0001). Specifically, survival was reduced by 10% for every 15 min delay of treatment until 3 h, at which point no benefit was demonstrated.
Conclusion: Patients with severe acute bleeding should be treated immediately, as even a short delay in treatment reduces the survival benefit of tranexamic acid.

ASCO Clinical Practice Guidelines for VTE Prophylaxis and Treatment in Patients with Cancer
J Clin Oncol 2020;38:496-520
Clinicians can offer thromboprophylaxis (apixaban, rivaroxaban, or LMWH) for:
- High-risk outpatients with cancer
- As options for VTE treatment
- For long-term anticoagulation (min. 6 mo; better efficacy profiles than vitamin K antagonists)
- Throughout hospitalization (patients with cancer and an acute medical condition)
- Major cancer surgery (prophylaxis starting prior and continuing for min. 7-10 d)

Initiation of Warfarin Therapy Requires Bridging with Heparin Therapy for 4-5 Days
10 mg loading dose of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state
Warfarin decreases Factor VII levels in first 48 h, INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after ~4 d)

Low-Risk Surgical Patients
<40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal, or thoracic surgery

Moderate-Risk Surgical Patients
>40 yr, >1 risk factor for VTE, GA >30 min

High-Risk Surgical Patients
>40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency, or other risk factors

High-Risk Medical Patients
Heart failure, severe respiratory disease, ischemic stroke or lower limb paralysis, confined to bed, and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD)

Hematologic Malignancies and Related Disorders

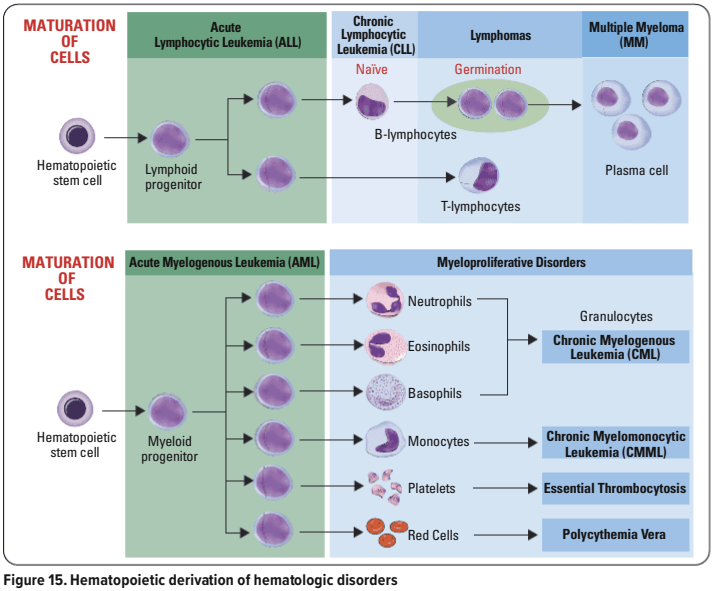

Figure 15. Hematopoietic derivation of hematologic disorders

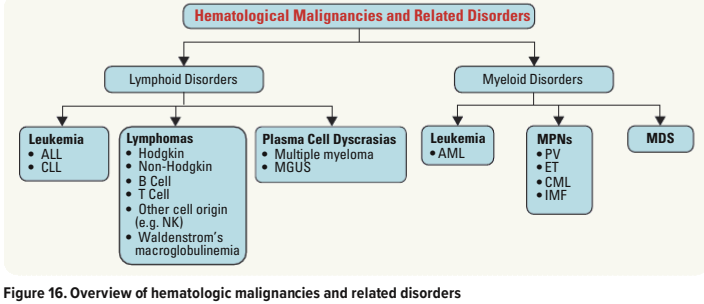

Figure 16. Overview of hematologic malignancies and related disorders

Leukemia: malignant cells arise in BM that may spread elsewhere (including blood, lymph nodes, and lymphoid tissue)
Lymphoma: malignant cells arise in lymph nodes and lymphoid tissues that may spread elsewhere (including blood and BM)
BUT the location where the malignant cells are found does not solely define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes)

Acute Leukemia
Definition (WHO): presence of 20% blast cells or greater in the peripheral blood or BM at presentation
Classification: divided into myeloid (AML) and lymphoid (ALL) depending on whether blasts are myeloblasts or lymphoblasts, respectively

Typical Age of Presentation of Leukemias
ALL: Children and older adults
CML: 40-60 yr
AML, **CLL**: >60 yr

Auer rods are pathognomonic for AML

Basic Initial Workup for all Hematologic Malignancies:
1. ALL WOMEN OF CHILDBEARING AGE must have a b-HCG before initiation of treatment of any cancer diagnosis
2. ALL PATIENTS MUST HAVE Hepatitis B surface antibody (HBsAb), Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb) collected irrespective of cancer diagnosis and must be treated to avoid reactivation
3. All aggressive lymphoma patients must be screened for HIV
4. All patients must be screened for TB risk factors

Cure: survival that parallels age-matched population
Complete Remission: tumour load below threshold of detectable disease (normal peripheral blood film, normal BM with <5% blasts, normal clinical state)

Myeloid Malignancies

Acute Myeloid Leukemia

Definition
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

Epidemiology
- incidence increases with age; median age of onset is 65 yr; accounts for 80% of acute adult leukemias
- accounts for 10-15% of childhood leukemias

Risk Factors
- male, older age, smoking, obesity, MDS, benzene, radiation, Down syndrome, alkylating agents, and radiation therapy as treatment for previous malignancy

Pathophysiology
- etiology subdivided into:
  - primary: *de novo*
  - secondary: prior hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to:
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood – risk of leukostasis
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; TLS
- cancer stem cells thought to play key role in development and progression, subpopulation of self-renewing cancer cells with unique surface markers such as CD34, CD38, CD123

Clinical Features
- signs and symptoms develop over a period of weeks
- manifestations of BM failure
  - anemia, thrombocytopenia (associated with DIC in APL), neutropenia (and infection/fever)
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - CNS extramedullary involvement: confusion or altered mental status
  - hepatosplenomegaly (also present in ALL)
  - lymphadenopathy
  - skin: leukemia cutis
  - eyes: hemorrhages and/or whitish plaques, Roth spots, cotton wool spots, and vision changes (uncommon)
- leukostasis/hyperleukocytosis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, and priapism
  - more commonly associated with AML than ALL
- metabolic effects (aggravated by treatment)
  - TLS
    - increased uric acid → nephropathy, gout
    - release of phosphate → decreased Ca^{2+}, decreased Mg^{2+}
    - release of procoagulants → DIC (higher risk in APL)
  - hyperkalemia pre-treatment from blastic proliferation and spontaneous TLS, further hyperkalemia after treatment (from lysed cells). Note – some forms of AML can present with hypokalemia due to secreted muramidase that causes K+ wasting from renal tubules

Investigations
- blood work
  - CBC: anemia, thrombocytopenia, variable WBC (most often cytopenias + blasts)
  - INR up, aPTT up, FDP up, fibrinogen down (in case of DIC)
  - increased LDH, increased uric acid, increased PO_4^{3-} (released by leukemic blasts), decreased Ca^{2+}, increased/decreased K^+
  - baseline renal and liver function tests
  - if considering treatment: screen for HBV, HCV, HIV, CMV serology
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- BM aspirate for definitive diagnosis
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytogenetic, and/or immunophenotypic features are used to establish lineage and maturation
- CXR to rule out pneumonia; ECG, MUGA scan prior to chemotherapy (cardiotoxic)

Treatment
- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
- patients who are not eligible for intensive chemotherapy can be treated with low-dose cytarabine and hypomethylating agents in combination with venetoclax (BCL-2 inhibitor)
- all AML subtypes are treated similarly, except APL with t(15:17) translocation
  1. **induction**: chemotherapy to induce complete remission of AML
     - several possible regimens
     - patients with poor response to initial induction therapy – worse prognosis
     - supportive care - management of TLS and DIC, febrile neutropenia/infections, transfusion support (including platelet transfusions if $<10 \times 10^9$/L)
  2. **consolidation**: to prevent recurrence
     - intensive consolidation chemotherapy

- stem cell transplantation – allogeneic (younger patients with better performance status and/or adverse cytogenetics)

- supportive care
  - fever: pan-cultures, CXR, and start broad-spectrum antibiotics
  - platelet and RBC transfusions
  - prevention and treatment of metabolic abnormalities
    - allopurinol, rasburicase for prevention/management of hyperuricemia
  - leukostasis
    - needs immediate cytoreductive therapy (i.e. hydroxyurea)
  - treatment strategy for APL
    - APL is an emergency as DIC is often present at diagnosis
    - ATRA added to induce differentiation (should be started ASAP if APL is in the differential); arsenic trioxide and ATRA combination therapy for APL is superior to traditional chemotherapy

Prognosis

- achievement of first remission
  - 70-80% if ≤60 y/o, 50% if >60 y/o
  - median survival 12-24 mo
  - prognosis depends on cytogenetics, age, performance status, prior cytotoxic agents, or radiation therapy

Myelodysplastic Syndromes

Definition

- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias and a variable risk of transformation to acute leukemias
- syndromes defined according to WHO classifications

Pathophysiology

- disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in BM (usually hypercellular); formed elements sometimes exhibit morphological and functional defects
- intramedullary apoptosis: programmed cell death within BM
- both processes lead to reduced mature cells in periphery
- <30% develop AML

Risk Factors

- elderly, post-chemotherapy, exposures (benzene, tobacco, radiation), inherited genetic abnormalities
- incidence: 50 persons per million per year, rises to 200-400 per million per year for age 70 or older

Clinical Features

- highly variable, commonly presents with symptoms of anemia (fatigue and dyspnea), thrombocytopenia (bruising, bleeding, or petechiae), and neutropenia (recurrent infections) over months-years

Investigations

- diagnosed by:
  - anemia ± thrombocytopenia ± neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bi-lobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size, and cytoplasm (e.g. giant hypogranular platelets)
- BM aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
  - BM: dysplastic and often normocellular/hypercellular
  - cytogenetics: high-risk (partial or total loss of chromosome 7) and complex (>3 abnormalities)

Treatment

- low-risk of transformation to acute leukemia (Revised International Prognostic Scoring System (IPSS-R) Very Low or Low)
  - EPO stimulating agents weekly is first line in reducing transfusion requirements (EPO level must be <500 IU/L)
  - if 5q deletion based on cytogenetics: lenalidomide PO
  - supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- high-risk of transformation to acute leukemia (IPSS-R Intermediate, High, or Very High)
  - supportive care (transfusion support)
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacitidine)
  - consider stem cell transplantation according to patient factors (age, frailty, overall health)

Prognosis
- IPSS-R uses 5 factors to estimate mean survival:
  - cytology, % BM blasts, Hb, platelets, and ANC
  - based on the calculated score, a patient's MDS prognostic risk is "Very Low", "Low", "Intermediate", "High", or "Very High" with a mean survival of 8.7, 5.3, 3.0, 1.6, and 0.8 yr, respectively

Myeloproliferative Neoplasms

Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (erythrocytes, platelets, and other cells of myeloid lineage)

Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)

Prognosis
- may develop marrow fibrosis with time
- all disorders may progress to AML

Table 30. Chronic Myeloproliferative Disorders

	CML	PV	IMF	ET
Hct	↓/N	↑↑	↓	N
WBC	↑↑	↑	↑/↓	N
Plt	↑/↓	↑	↑/↓	↑↑↑
Marrow Fibrosis	±	±	+++	±
Splenomegaly	+++	+	+++	+
Hepatomegaly	+	+	++	–
Genetic Association	BCR-ABL mut.	JAK2 mut. (96%)	JAK2 mut. (~50%) CALR mut. (~30%)	JAK2 mut. (~50%) CALR mut. (~30%)

Chronic Myeloid Leukemia

Definition
- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

Epidemiology
- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

Pathophysiology
- Ph chromosome
  - translocation between chromosomes 9 and 22 is necessary and sufficient to result in CML
  - the c-Abl proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (BCR) of chromosome 22 to produce BCR-ABL fusion gene, a constitutively active tyrosine kinase

Clinical Features
- 3 clinical phases
  - chronic phase: 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - accelerated phase: impaired neutrophil differentiation
    - circulating blasts (10-20%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytopenia <100 x 10^9/L or thrombocytosis
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
  - blast crisis: more aggressive course, blasts fail to differentiate
    - blasts (>20%) in peripheral blood or BM; reflective of acute leukemia (1/3 ALL, 2/3 AML)
- clinical features
  - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
  - nonspecific symptoms
    - fatigue, weight loss, malaise, excessive sweating, fever

Use of Epoetin and Darbepoetin in Patients with Cancer
Blood 2008;111:25-41
Clinical practice guideline update by American Societies of Hematology and Clinical Oncology (2010).
Initial Recommendations
1. Initiate an ESA when Hb is 100 g/L (10 g/dL) in patients with palliative chemotherapy-associated anemia to decrease the need for transfusions
2. Discontinue ESAs when patient not responding to treatment beyond 6-8 wk
3. Monitor iron stores and supplement iron intake for ESA-treated patients when necessary
4. Use ESAs cautiously with chemotherapy or in patients with an elevated risk for thromboembolic complications
5. It is not recommended that ESA be used for therapy in patients with cancer who are not receiving chemotherapy as it increases thromboembolic risks and lowers survival rate. Patients with low-risk myelodysplasia are an exception

MDS ineffective maturation
MPN overproduction of mature cells

Basophilia is uncommon in other medical conditions

Chronic Myeloproliferative Neoplasms: 11-Year Follow-Up of Patients Receiving Imatinib for the First-Line Treatment of CML
NEJM 2017;376:917-927
Study: Long-term outcomes of imatinib treatment for chronic myeloid leukemia.
Methods: 1106 patients with Ph-positive CML in the chronic phase were randomized 1:1 to imatinib or interferon alpha plus cytarabine. Crossover to imatinib was allowed if no response by 6 mo or major cytogenetic response by 12 mo.
Results: Assessing the imatinib arm after a median of 11 years of follow-up, the complete cytogenetic response rate was 83%. Among patients who attained a major molecular response after 18 mo of imatinib therapy, the overall survival at 10 years was 93% and freedom from CML-related deaths was 100%.
Conclusion: This 11-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.

- secondary to splenic involvement
  - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
  - splenomegaly (most common physical finding)
- anemia
- bleeding: secondary to platelet dysfunction
- pruritus, PUD: secondary to increased blood histamine
- leukostasis, priapism, encephalopathy: secondary to very elevated WBC (rare)

Investigations

- CBC with differential
  - elevated WBCs, decreased/normal RBCs, increased/decreased platelets, increased basophils
  - WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
- peripheral blood film
  - leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  - presence of different mid-stage progenitor cells differentiates it from AML
- BM biopsy
  - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
- molecular and cytogenetic studies of BM or peripheral blood for Ph chromosome (or BCR-ABL transcripts)
- abdominal imaging for spleen size

Treatment

- **prophylactic**: allopurinol
- **chronic phase**
  - imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for BCR-ABL. 2nd/3rd generation can be used as first line therapy
    - if loss of response or intolerance (~40%), trial of 2nd or 3rd generation TKIs: dasatinib, nilotinib, or bosutinib. Note: ponatinib only provided for the T315I mutation
  - interferon-α: may improve response to TKIs; typically now only used for pregnant patients
  - hydroxyurea in palliative setting to reduce WBCs
- **accelerated phase or blast phase**
  - for imatinib-naive patients, use imatinib
  - refer for clinical trial or 2nd/3rd generation TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard induction for acute leukemia
- stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones
- treatment success is monitored based on therapeutic milestones
  - hematologic: improved WBC and platelet counts, reduced basophils
  - cytogenetic: undetectable Ph chromosome in the BM
  - molecular: reduction/absence of BCR-ABL transcripts in periphery and marrow

Prognosis

- survival dependent on response
  - those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  - those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
- acute phase (blast crisis – usually within 3-5 yr of presentation if untreated CML)
  - 2/3 acute phase CML have cellular features similar to AML
    - unresponsive to remission induction
  - 1/3 acute phase CML have cellular features similar to ALL
    - remission induction (return to chronic phase) achievable

Polycythemia Vera

Definition

- stem cell disorder characterized by elevated RBC count (erythrocytosis) ± increased white cell and platelet production
- diagnosis (WHO 2016) requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion
  - Major Criteria
    1. Hb >165 g/L in men, >160 g/L in women, OR Hct >49% in men, >48% in women, OR increased red cell mass (>25% above mean normal predicted value)
    2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
    3. presence of JAK2 V617F or JAK2 exon 12 mutation
  - Minor Criterion
    1. serum EPO level below reference range for normal (must have the first two major criteria if using EPO level)

Erythromelalgia is a pathognomonic microvascular thrombotic complication in PV and ET

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera
NEJM 2013;368:22-33
Study: Prospective, RCT, mean follow-up of 28.9 mo. Blinding not described.
Population: 365 patients with JAK2-positive polycythemia vera being treated with phlebotomy, hydroxyurea, or both.
Intervention: Patients were randomized to a target hematocrit <45% (low-hematocrit group) or 45-50% (high-hematocrit group).
Outcome: Composite of time until death from cardiovascular causes of major thrombotic events.
Results: The hazard ratio (HR) for the primary outcome was 3.91 (95% CI 1.45-10.53, P=0.007), while the HR for the primary outcome plus superficial venous thrombosis was 2.69 (95% CI 1.19-6.12, P=0.02) for the high-hematocrit vs. low-hematocrit group.
Conclusions: The hematocrit target of <45% was associated with a lower incidence of CV death, major thrombotic events, and superficial venous thrombosis in patients with polycythemia vera.

Clinical Features
- symptoms are secondary to high red cell mass and hyperviscosity (see *Erythrocytosis, H7*)
- thrombotic complications: DVT, PE, Budd-Chiari (hepatic vein thrombosis), portal vein thrombosis, thrombophlebitis, increased incidence of stroke/TIA, and MI
  - due to increased blood viscosity, increased platelet number, and/or activity
  - bleeding complications: epistaxis, gingival bleeding, ecchymoses, and GI bleeding
  - if high platelet counts: associated with acquired VWD (although seen more with ET)
- erythromelalgia (burning pain in hands and feet and erythema of the skin)
  - associated with platelets >400 x 10^9/L
  - pathognomonic microvascular thrombotic complication in PV and ET
- pruritus, especially after warm bath or shower (40%) due to cutaneous mast cell degranulation and histamine release
- epigastric distress, PUD
  - due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity
- gout (hyperuricemia), due to increased cell turnover
- characteristic physical findings
  - plethora (ruddy complexion) of face (70%), palms
  - splenomegaly (70%), hepatomegaly (40%)

Investigations *(see Erythrocytosis, H7)*
- must rule out secondary polycythemia if high EPO level

Treatment
- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- ruxolitinib for those with insufficient response or intolerance to hydroxyurea
- low-dose ASA (for antithrombotic prophylaxis, will also treat erythromelalgia)
- allopurinol: as needed
- antihistamines: as needed

Prognosis
- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)

Idiopathic Myelofibrosis

Definition
- excessive BM fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood, and hepatosplenomegaly

Epidemiology
- rare, median age at presentation is 65 yr

Pathophysiology
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (see below)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

Clinical Features
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety and severe left upper quadrant pain
- hepatomegaly (70%) → may develop portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

Investigations
- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B_{12} (2° to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets, and megakaryocyte fragments
- molecular test: JAK2 (70%) and CALR(25%) mutations
- BM aspirate: "dry tap" in as many as 50% of patients (no marrow spicules aspirated)
- BM biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

Efficacy and Safety of Low-dose Aspirin® in Polycythemia Vera
NEJM 2004;350:114-124
Study: Double-blind, placebo-controlled, RCT.
Participants: 518 patients with polycythemia vera (PV) with no clear indication for, or contraindication to, ASA therapy.
Intervention: Patients received either low-dose ASA 100 mg daily (n=253) or placebo (n=265) and were followed for up to 5 yr.
Primary Outcome: Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus PE and major venous thrombosis.
Results: Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41; P=0.09 and RR 0.4; P=0.03, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.
Conclusion: Low-dose ASA can safely prevent thrombotic complications in patients with PV.

Ruxolitinib Versus Standard Therapy for the Treatment of Polycythemia Vera
NEJM 2015;372:426-35
Purpose: To evaluate the efficacy and safety of ruxolitinib vs. standard therapy in patients with PV who had insufficient responses or intolerable side effects with hydroxyurea.
Methods: 222 phlebotomy-dependent patients with splenomegaly were randomly assigned to receive ruxolitinib or standard therapy.
Primary Outcome: Hematocrit control through week 32 and spleen volume reduced ≥35% at week 32.
Results: 21% of patients on ruxolitinib vs. 1% of those on standard-therapy achieved the primary outcome (P<0.001). 60% of patients on ruxolitinib and 20% on standard therapy achieved hematocrit control. ≥35% reduction in spleen volume was seen in 38% and 1% of patients in the two groups, respectively. Compared to standard-therapy, ruxolitinib was associated with a significantly greater rate of complete hematologic remission (24% vs. 9%; P=0.003).
Conclusion: Ruxolitinib was superior to standard therapy in controlling hematocrit, reducing the spleen volume, and improving symptoms associated with PV in patients who had insufficient responses or intolerable side effects with hydroxyurea.

Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PV or ET

A "leukoerythroblastic" blood film (RBC and granulocyte precursors) implies BM infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF)

IMF typically has a dry BM aspirate and teardrop RBCs (aspiration gives no blood cells)

Treatment
- allogeneic stem cell transplant is potentially curative
- JAK2 inhibitors (ruxolitinib, fedratinib, or hydroxyurea)
- symptomatic treatment
  - transfusion for anemia
  - EPO: 30-50% of patients respond
  - androgens for anemia (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, and systemic symptoms
    - interferon-α (as second line therapy)
    - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis and symptomatic splenomegaly

Prognosis
- Dynamic International Prognostic Scoring System (DIPSS) Plus for IMF uses 5 risk factors along with karyotype, platelet count, and transfusion status to predict survival
  - presence of constitutional symptoms; age >65; Hb <100 g/L; leukocyte count >25000/mm ^{3}; circulating blast cells ≥1%
  - based on the calculated score, a patient's IMF is categorized as "low", "intermediate 1", "intermediate 2", or "high" with a mean survival of 185, 78, 35, and 16 mo, respectively
  - eligible patients with intermediate 2 or high risk DIPSS are considered for allogeneic stem cell transplant
- risk of transformation to AML (8-10%)

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis
NEJM 2012;366:799-807
Study: Double-blinded RCT of 309 patients with myelofibrosis randomized to ruxolitinib or placebo.
Outcome: Primary outcome was reduction in spleen volume of >35% at 24 wk. Secondary outcomes were durability of response, symptom burden, and overall survival.
Results: A greater proportion of patients on ruxolitinib had reduction in spleen volume >35% (41.9% vs. 0.7%) and this was sustained in 67% at 48 wk. Ruxolitinib also led to greater symptom improvement (45% vs. 5.3%) and less mortality (13 vs. 24). There was no difference in rate of discontinuation due to adverse events (11.0% vs. 10.6%) but anemia and thrombocytopenia were more common with ruxolitinib.
Conclusions: Ruxolitinib reduced spleen size, and improved symptoms and survival, compared with placebo.

Essential Thrombocythemia

Definition
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocythemia

Epidemiology
- increases with age; F:M=2:1, → F=M at older

Diagnosis (2008 WHO Criteria Revised in 2016) requires meeting all four criteria
1. sustained platelet count >450 x 10^9/L
2. BM biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. not meeting WHO criteria for PV, primary myelofibrosis, BCR-ABL CML, or MDS or other myeloid neoplasms
4. most patients have a mutation in JAK2 V617F, CALR, or MPL. A minority (~10%) have a mutation in some other gene, which causes proliferation (hence "clonal marker")

Etiology of Secondary Thrombocythemia
Infection
Inflammation (IBD, arthritis)
Malignancy
Hemorrhage
Iron deficiency
Hemolytic anemia
Post-splenectomy
Post-chemotherapy
Drugs (vinca alkaloids)

Clinical Features
- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation → microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI; associated with platelets >1000 x 10^9/L)
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

Investigations
- CBC: increased platelets; may have abnormal platelet aggregation studies or VWD studies
- JAK2 (and other) mutational assays
- BM hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased K^+, increased PO_4^{3-} (2º to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

Treatment
- low dose ASA
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st-line therapy), anagrelide, interferon-α, or 32P (age >80 or lifespan <10 yr)

There is an asymptomatic "benign" form of essential thrombocythemia with a stable or slowly rising platelet count; treatment includes observation, ASA, sulfinpyrazone, or dipyridamole

Lymphoid Malignancies

Acute Lymphoblastic Leukemia

75% of ALL occurs in children <6 yr; second peak at age 40

Definition
- malignant disease of the BM in which early lymphoid precursors proliferate and replace normal hematopoietic cells
- WHO subdivides ALL into two types depending on cell of origin
  - 1. B-cell: precursor B lymphoblastic leukemia
  - 2. T-cell: precursor T lymphoblastic leukemia
- the French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged as morphology is not prognostic

Clinical Features
- see *Acute Myeloid Leukemia, H39* for full list of symptoms
- distinguish ALL from AML based on *Table 32*
- clinical symptoms usually secondary to:
  - BM failure: anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), and thrombocytopenia
  - organ infiltration: tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations
- >20% BM or peripheral blood lymphoblasts, with samples collected for flow cytometry, cytogenetics, and molecular studies
- Ph chromosome in ~25% of adult ALL cases
- CBC: increased leukocytes >100 x 10^9/L (occurs in 50% of patients); neutropenia, anemia, or thrombocytopenia
- screen for TLS: increased uric acid, K^+, PO_4^{3-}, low Ca^{2+}, high LDH
- screen for DIC: PT, aPTT, fibrinogen
- CXR: patients with ALL may have a mediastinal mass
- CT C/A/P and testicular ultrasound to screen for extranodal disease
- mandatory lumbar puncture to assess for CNS involvement (ensure adequate platelet count and PT/PTT and delay until blasts have cleared from peripheral blood) at the time treatment is initiated
- HIV, HBV, HCV serologies, CMV Ab testing

Treatment
- eliminate abnormal clonal cells
  1. induction chemotherapy: to induce complete remission, <5% blasts (restore normal hematopoiesis)
  2. consolidation and/or intensification of chemotherapy
     - consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
     - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. maintenance chemotherapy: low dose intermittent chemotherapy over prolonged period (1 yr) to prevent relapse
  4. prophylaxis: CNS radiation therapy or methotrexate (intrathecal or systemic)
- hematopoietic stem cell transplantation (for certain indications): potentially curative (due to pre-transplant myeloablative chemoradiation and post-transplant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high
  - if BCR-ABL positive, tyrosine kinase inhibitors started up front and given continuously
  - in relapse setting, CAR T-cell therapy, inotuzumab, or blinatumomab
- CAR T-cell therapy
  - extraction of patient's own T-cells, genetic modification of T-cells to produce Chimeric Antigen Receptors (CARs) that recognize antigens presented selectively on cancer cell surface (often CD19 in ALL)
  - most effective in treating diffuse large B-cell lymphoma and CD19-positive ALL
  - first approved in Canada in 2018, currently of limited utility in treating other types of hematologic malignancies and solid tumours

Treatment of ALL vs. AML
No proven benefit of maintenance chemotherapy in AML
No routine CNS prophylaxis in AML

Prognosis
- depends on response to initial induction, minimal residual disease testing, or if remission is achieved following relapse
- good prognostic factors: young, WBC <30 x 10^9/L, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 75% long-term remission (>5 yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of BCR-ABL fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5 yr survival

Table 31. Differentiating AML From ALL

AML	ALL
Big people (adults)	Small people (kids)
Big blasts	Small blasts
Big mortality rate	Small mortality rate (kids)
Lots of cytoplasm	Less cytoplasm
Lots of nucleoli (3-5)	Few nucleoli (1-3)
Lots of granules and Auer rods	No granules and no Auer rods
Myeloperoxidase, Sudan black stain	PAS (periodic acid-Schiff)
Maturation defect beyond myeloblast or promyelocyte	Maturation defect beyond lymphoblast

To Differentiate AML from ALL: Remember Big and SmALL

Lymphomas

Definition

- collection of lymphoid malignancies in which malignant lymphocytes accumulate in lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease, and constitutional symptoms

Table 32. Ann Arbor System for Staging Lymphomas

Stage	Description
I	Involvement of a single lymph node region or extralymphatic organ/site (Stage IE)
II	Involvement of ≥2 lymph node regions or an extralymphatic site and ≥1 lymph node regions on same side of diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Diffuse involvement of one or more extralymphatic organs including BM

American Society of Hematology Choosing Wisely Recommendation
Limit surveillance CT scans in asymptomatic patients after curative-intent treatment for aggressive lymphoma

- subtypes
  A = absence of B-symptoms (*see Approach to Lymphadenopathy, H12*)
  B = presence of B-symptoms

Table 33. Chromosome Translocations

Translocation	Gene Activation	Associated Neoplasm
t(2;5)	ALK1 mutation	Anaplastic large cell lymphoma
t(8;14)	c-Myc activation	Burkitt's lymphoma
t(14;18)	Bcl-2 activation	Follicular lymphoma
t(11;14)	Overexpression of cyclin D1 protein	Mantle cell lymphoma
t(11;18)	MALT1 activation	Mucosa-associated lymphoid tissue (MALT)

- Ann Arbor staging can be used for both Hodgkin and non-Hodgkin lymphoma, but grade/histology is more important for non-Hodgkin lymphoma because the outcome differs significantly depending on type of lymphoma
- Prognostic scores are different for indolent vs. aggressive lymphomas
- Highly aggressive lymphomas act like acute leukemias

Hodgkin Lymphoma

Definition

- malignant proliferation of lymphoid cells with Reed-Sternberg cells

Epidemiology

- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases and causal role not determined

Hodgkin is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells

Clinical Features

- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
- splenomegaly (50%) ± hepatomegaly
- mediastinal mass
  - found on routine CXR, may be symptomatic (cough)
  - rarely may present with superior vena cava syndrome and pleural effusion
- systemic symptoms
  - B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C, or night sweats for ≥2 wk without evidence of infection), extreme fatigue especially in widespread disease, and pruritus
- non-specific/paraneoplastic
- starts at a single site in lymphatic system (node) and spreads first to adjacent nodes
  - disease progresses in contiguity with lymphatic system

Hodgkin lymphoma classically presents as a painless, non-tender, firm, rubbery enlargement of superficial lymph nodes, most often in the cervical region

Investigations

- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, lymphopenia, platelets normal or increased in early disease, and decreased in advanced disease

- biochemistry
  - HIV, HBV, HCV serologies
  - liver enzymes and/or LFTs (liver involvement)
  - renal function tests (prior to initiating chemotherapy)
  - ALP, Ca^{2+}(bone involvement)
  - ESR (prognosis), LDH (staging, monitor disease progression)
- imaging
  - CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), and PET scan
  - cardiac function assessment (MUGA scan or echocardiography): for patients at high-risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA), treatment can be cardiotoxic
  - PFTs: if history of lung disease (COPD, smoking, and previous radiation to lung)
- excisional lymph node or core biopsy confirms diagnosis
- BM biopsy to assess marrow infiltration (only necessary if B-symptoms, PET positive marrow on imaging, or cytopenia)

Treatment

Treatment of HL depends on stage; treatment of NHL depends on histologic subtype

- stage I-II: chemotherapy (ABVD (adriamycin, bleomycin, vinblastine, dacarbazine)) followed by involved field or involved site radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD, Brentuximab-AVD, or BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone)) ± XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy and autologous stem cell transplant, anti-CD30 Ab therapy
  - PET scan results essential in assessing disease response

Complications of Treatment

- cardiac disease: secondary to XRT, adriamycin cardiomyopathy (1% of patients)
- pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
- infertility: <3% with ABVD (important to discuss sperm banking/egg retrieval prior to initiation of chemotherapy)
- secondary malignancy in irradiated field
  - <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  - solid tumours of lung or breast (>8 yr after treatment)
  - non-Hodgkin lymphoma
- hypothyroidism: post XRT

Prognosis

International Prognostic Factors Project 1998

Prognostic Factors	FFP
0	84%
1	77%
2	67%
3	60%
4	51%
5-7	42%

FFP = freedom from progression at 5 yr

- Hasenclever adverse prognostic factors:
  1. serum albumin <40 g/L
  2. Hb <105 g/L
  3. male
  4. stage IV disease
  5. age ≥45 yr
  6. leukocytosis (WBC >15 x 10^9/L)
  7. lymphocytopenia (lymphocytes <0.06 x 10^9/L or <8% of WBC count or both)
- each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)

Non-Hodgkin Lymphoma

Definition

- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

Classification

- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, and mantle cell lymphoma
  - WHO/REAL classification system: 3 categories of NHLs based on natural history
    1. indolent (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, and mantle cell lymphoma
    2. aggressive (~50% of NHL): e.g. diffuse large B-cell lymphoma
    3. highly aggressive (~5% of NHL): e.g. Burkitt's lymphoma
  - T-cell NHL: e.g. mycosis fungoides (indolent TCL of the skin), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), and anaplastic large cell lymphoma

Clinical Features

- painless superficial lymphadenopathy, usually >1 lymph node region, rapid growth in aggressive lymphomas
- can have localized or widespread adenopathy (more common in indolent NHL)
- constitutional symptoms are less common in Hodgkin lymphoma
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when BM is involved
- abdominal signs ± hepatosplenomegaly, retroperitoneal, and mesenteric involvement

- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement: most commonly GI tract, testes, bone, and kidney
- CNS involvement in 1% (often with HIV, testicular DLBCL, or >2 extranodal sites)

Investigations
- CBC
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia rare (more common in CLL)
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic blood film
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood only if lymphocytosis is present
- biochemistries, HIV, HBV, HCV serologies
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease and poor prognostic factor)
- SPEP and immunoglobulin quantitation (screen for high IgM monoclonal protein and hyperviscosity in indolent lymphomas, specifically lymphoplasmacytic lymphoma)
- staging: CT neck, chest, abdomen, pelvis, and BM biopsy
- PET imaging pre- and post-therapy to ensure post treatment remission
- diagnosed by:
  - lymph node biopsy: excisional biopsy is preferred, core biopsy (FNA is unreliable)
  - BM biopsy: sub-optimal mode of diagnosis as BM is involved in only 30% of high-grade lymphomas

Treatment
- indolent NHL, localized disease (e.g. stage I or II)
  - radiotherapy to primary site and adjacent nodal areas
  - splenectomy: splenic marginal zone lymphoma
- goal of treatment in stage III or IV indolent NHL is symptom management
  - watchful waiting
  - radiation therapy for localized symptomatic disease
  - bendamustine plus rituximab, an anti-CD20 Ab, is superior to CHOP and rituximab (CHOP-R) for advanced stage disease
  - obinutuzumab (novel anti-CD20 Ab) is superior to rituximab for advanced stage follicular lymphoma (GALLIUM Trial)
- aggressive lymphoma: goal of treatment is curative
  - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  - radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites involved (e.g. testes)
  - relapse, resistant to therapy: high dose chemotherapy, autologous SCT, CAR T-cell therapy in second relapse
- highly aggressive lymphoma
  - Burkitt lymphoma: short bursts of intensive chemotherapy; "CODOX-M" chemotherapy regimen also often used ± IVAC with rituximab
  - CNS prophylaxis and (TLS) prophylaxis

NHL: Associated Conditions
Immunodeficiency (e.g. HIV)
Autoimmune diseases (e.g. SLE)
Infections (e.g. EBV)

Common Chemotherapeutic Regimens
R-CHOP: cyclophosphamide, hydroxydoxorubicin (Adriamycin®), vincristine (Oncovin®), prednisone
ABVD: adriamycin, bleomycin, vinblastine, dacarbazine
BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone

Complications
- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- bowel perforation
- (TLS particularly in very aggressive lymphoma); see *Tumour Lysis Syndrome, H54*

Prognosis
- follicular lymphoma: Follicular Lymphoma International Prognostic Index is used: age >60; >4 nodal areas; >6 cm nodal areas; elevated LDH; Lugano stage III-IV; Hb <120 g/L; high β-2 microglobulin; BM involvement
  - based on calculated risk, mean 5 yr survival ranges from 53-91%
  - rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
- diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrod 2-4); elevated LDH; >1 extranodal site
  - based on calculated risk, mean 5 yr survival ranges from 26-73%
  - ~40% rate of cure

Table 34. Characteristics of Select Non-Hodgkin Lymphomas

	Follicular Lymphoma	DLBCL	Burkitt Lymphoma	Mantle Cell Lymphoma
Percentage of NHLs	22-30%	33%	<1% adult NHLs 30% childhood NHLs	6%
Genetic Mutation	Bcl-2 activation	Bcl-2, Bcl-6, Myc rearrangements	c-Myc activation	Overexpression of cyclin D1 (Bcl-1 activation)
Classification	Indolent	Aggressive (high-grade)	Very aggressive	Indolent
Risk Factors	Middle-age – elderly	Previous CLL (Richter's transformation: 5% CLL patients progress to DLBCL)	Endemic: African origin, EBV-associated Sporadic: no EBV HIV-related: AIDS-defining illness	Male (M:F=4:1)
Clinical Features	Widespread painless LAD* ± BM involvement Frequent transformation to aggressive lymphoma Very responsive to chemoradiation treatment	Rapidly progressive LAD and extranodal infiltration 50% present at stage I/II, 50% widely disseminated	Endemic form: massive jaw LAD "Starry-sky" histology High-risk of tumour lysis syndrome upon treatment	Often presents as stage IV with palpable LAD Involvement of GI tract (lymphomatous polyposis), Waldeyer's Ring 5 yr survival 25% B symptoms present in ⅓ of patients

Malignant Clonal Proliferations of Mature B-Cells

Table 35. Characteristics of B-Cell Malignant Proliferation

	CLL	Lymphoplasmacytic Lymphoma	Myeloma
Cell Type	Lymphocyte	Plasmacytoid	Plasma cell
Protein	IgM if present	IgM	IgG, A, light chain (rarely M, D, or E)
Lymph Nodes	Very common	Common	Rare
Hepatosplenomegaly	Common	Common	Rare
Bone Lesions	Rare	Rare	Common
Hypercalcemia	Rare	Rare	Common
Renal Failure	Rare	Rare	Common
Immunoglobulin Complications	Common	Rare	Rare

Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality)

Chronic Lymphocytic Leukemia

Definition
- indolent disease characterized by clonal malignancy of mature B-cells

Epidemiology
- most common leukemia in Western world
- mainly older patients; median age 70 yr
- M>F

Pathophysiology
- accumulation of neoplastic lymphocytes in blood, BM, lymph nodes, and spleen

Clinical Features
- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C, or night sweats for ≥2 wk without evidence of infection), extreme fatigue
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (DAT positive), ITP, hypogammaglobulinemia ± neutropenia
- BM failure: late, secondary to marrow involvement by CLL cells

Investigations
- CBC: clonal population of B lymphocytes >5 x 10^9/L
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry characteristics of peripheral blood
  - CD5, CD20dim, CD23, light chain restriction
- cytogenetics: FISH (dictates response to therapy and prognosis) imaging must be done post-therapy to ensure post treatment remission

- BM aspirate
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis), or mixed (25%)

Natural History and Treatment

- natural history: indolent and incurable; most cases show slow progression
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- first line therapy is dictated by cytogenetic status and patient co-morbidities
  - observation if early, stable, asymptomatic
    - treatment options vary by region; commonly fludarabine + cyclophosphamide + rituximab (FCR) in fit patients age <65, with normal creatinine clearance and lack of 17p deletion/p53 disease
    - chlorambucil (or venetoclax + obinutuzumab in the elderly)
    - ibrutinib or acalabrutinib in patients with unmutated IgVH and/or 17p deletion/p53 positivity
  - autoimmune phenomena: corticosteroids, rituximab
  - radiotherapy for isolated bulky nodes
- molecular therapies
  - idelalisib – PI3K inhibitor
  - ibrutinib, acalabrutinib – BTK (Bruton's tyrosine kinase) inhibitor
  - venetoclax – Bcl-2 inhibitor

Smudge cells are artifacts of damaged lymphocytes from slide preparation

Prognosis

- 9 yr median survival, but varies greatly
- prognosis: Rai staging, Binet staging or Revised CLL International Prognostic Index (includes age >65, Rai/Binet stage, B2M, IGHV mutation status, 17p del or TP53 mutation positivity)

Complications

- BM failure
- immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia and impaired T-cell function)
- polyclonal or monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- 5% undergo Richter's transformation: aggressive transformation to diffuse large B-cell lymphoma (see *Table 35, H50*)

Multiple Myeloma

Definition

- neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
- usually a single clone of plasma cells, although biclonal myeloma also occurs; rarely non-secretory
- preceded by smoldering myeloma or MGUS

Epidemiology

- incidence 3 in 100000, most common plasma cell malignancy
- increased frequency with age; median age of diagnosis is 68 yr; M>F

Pathophysiology

- malignant plasma cells secrete monoclonal Ab
  - 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    - IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    - 15-20% produce free light chains or light chains alone found in either:
      - serum has an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      - urine has Bence-Jones protein
  - <5% are non-secretors

Multiple Myeloma

SLiM CRAB
Sixty percent plasma cells in BM specimen
Light chain ratio >100
MRI lytic lesion >0.5 cm
Calcium >2.80 mmol/L
Renal failure (Cr >176 mmol/L)
Anemia
Bony lesions (lytic lesions or osteoporosis felt to be caused by myeloma)

Amyloid
The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues
Found in a variety of clinical disorders and can cause systemic (e.g. MM (light chains)) or localized amyloidosis (e.g. Alzheimer disease (AB amyloid))

Clinical Features and Complications

- bone disease: pain (usually back), bony tenderness, pathologic fractures
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
  - increased bone resorption secondary to osteoclast activating factors such as PTHrP
- anemia: weakness, fatigue, pallor
  - secondary to BM suppression
- weight loss
- infections
  - usually *S. pneumoniae* and Gram-negatives
  - secondary to suppression of normal plasma cell function
- hypercalcemia: N/V, confusion, constipation, polyuria, and polydipsia
  - secondary to increased bone turnover

- renal disease/renal failure
  - most frequently causes cast nephropathy (see Nephrology, NP36)
- bleeding
  - secondary to thrombocytopenia, may see petechiae, purpura
  - can also be caused by acquired VWD
- extramedullary plasmacytoma
  - soft tissue mass composed of monoclonal plasma cells, purplish colour
- hyperviscosity: may manifest as headaches, stroke, angina, and MI
  - rare in MM as secondary to increased viscosity caused by IgM protein (more common in WM/LPL)
- amyloidosis
  - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
- neurologic disease: muscle weakness, pain, and paresthesias
  - radiculopathy caused by vertebral fracture and extramedullary plasmacytoma
  - spinal cord compression (10-20% of patients) is a medical emergency

Investigations

- CBC
  - normocytic anemia, thrombocytopenia, and leukopenia
  - rouleaux formation on peripheral film
- biochemistry
  - increased Ca^{2+}, increased ESR, decreased anion gap, increased Cr, albumin, β2-microglobulin, and LDH (as part of staging), and proteinuria (24 h urine collection)
- monoclonal proteins
  - SPEP: demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - UPEP: demonstrates light chains in urine = Bence-Jones protein (15% secrete only light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- BM aspirate and biopsy
  - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for fluorescence in situ hybridization (FISH) or cytogenetics (prognostic implications)
- skeletal series (x-rays), MRI if symptoms of cord compression, PET imaging to pick up lytic lesions in asymptomatic MM
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
- elevated β2-microglobulin and LDH, and low albumin, are poor prognosticators
  - HBV surface and core Abs, and HBV surface antigen

Diagnosis

- International Myeloma Working Group Criteria ("SLiM CRAB"):
  - ≥60% clonal plasma cells on BM examination
  - light chain ratio (free, involved/uninvolved) of ≥100 in the blood (involved must be at least 100 mg/L)
  - MRI with more than one bone lesion (≥5 mm)
  - CRAB – presence of end-organ damage related to plasma cell dyscrasia, such as:
    - increased serum Ca^{2+}
    - renal failure
    - anemia
    - lytic bone lesions

Treatment

- non-curative
- treatment goals
  - improvement in quality of life (improve anemia, reverse renal failure, prevent fractures)
  - prevention of progression and complications
  - increase overall survival
- autologous transplant if ≤70 yr
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents (i.e. IMIDs or PIs)
- transplant ineligible if >70 yr or comorbidities
  - pending on patient comorbidities can include a combination of: melphalan, prednisone, cyclophosphamide, PI (i.e. bortezomib), IMIDs (revlimid), anti-CD38 agents (e.g. daratumumab)
- supportive management
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, EPO for anemia, and DVT prophylaxis
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities, and preferences

Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis

Light Chain Disease

- 15% of MM produce only light chains
- Renal failure is a major problem
- Kappa > lambda light chain has better prognosis

Serum Free Light Chain Ratio is an Independent Risk Factor for Progression in MGUS
Blood 2005;106:812-817
Purpose: To determine whether the presence of monoclonal free kappa or lambda immunoglobulin light chains in MGUS increases the risk of progression to malignancy.
Methods: Retrospective study with median follow-up of 15 yr. Baseline serum samples obtained from 1383 MGUS patients seen at the Mayo clinic between 1960-1994. 1148 baseline samples were obtained within 30 d of diagnosis.
Results: Malignant progression had occurred in 87 (7.6%) patients. In 379 (33%) patients, an abnormal serum free light chain (FLC) ratio was detected. There was a significantly higher risk of progression in patients with an abnormal FLC ratio relative to patients with a normal ratio (hazard ratio, 3.5; 95% CI 2.3-5.5; P<0.001). This finding was independent of the size and type of the serum monoclonal (M) protein. In high-risk MGUS patients (abnormal serum FLC ratio, non-IgG MGUS, high serum M protein level [≥1.5 gm/dL]), the risk of progression at 20 yr was 58% compared to 37% in high-intermediate-risk MGUS (two risk factors), 21% low-intermediate risk (with one risk factor), and 5% low-risk (no risk factors).
Conclusions: The presence of an abnormal FLC ratio is a clinically and statistically significant predictor of progression in MGUS. The low-risk subset of patients with MGUS accounts for 40% of all MGUS patients and have a small lifetime risk of progression, thus less follow-up can be justified.

Prognosis
- International Staging System (ISS) (β2-microglobulin and albumin) used to stage and estimate prognosis
- revised ISS for risk stratification: combination of original ISS, cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy), and LDH
- median survival based on stage, usually 5-10 yr

Monoclonal Gammopathy of Unknown Significance

Definition
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr
  - asymptomatic

Diagnosis
- presence of a serum monoclonal protein (M protein) at a concentration <30 g/L
- <10% plasma cells in BM
- absence of SLiM CRAB
- 0.3-1% of patients develop a hematologic malignancy each yr
  - patients with M protein peak ≥15 g/L, abnormal free light chain ratio, or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with abnormal serum free light chains ratio are at increased risk of malignant transformation
- monitor with history q6-12 mo, physical, CBC, Cr, calcium, albumin, LDH, and SPEP (considered pre-malignant)

Lymphoplasmacytic Lymphoma

Definition
- LPL/Waldenstrom's macroglobulinemia
- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein

Clinical Features
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, and cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, and retinal lesions
- key complication to avoid: hyperviscosity syndrome
  - because IgM (unlike IgG) are large and confined mainly to intravascular space

Investigations and Diagnosis
- BM shows plasmacytoid lymphocytes
- bone lesions usually not present
- blood work rarely shows hypercalcemia
- cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, and high ESR if hyperviscosity not present
- HBV, HCV serologies (note: can be associated with HCV; HCV eradication can put LPL into remission)

Waldenstrom's macroglobulinemia accounts for 85% of all cases of hyperviscosity syndrome

Treatment
- chemotherapy + rituximab (most commonly bendamustine + rituximab)
- if HCV positive – treat HCV prior to a trial of chemotherapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

Definition
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum Igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases

Clinical Features
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, and stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

Treatment
- plasmapheresis, chemotherapy

Tumour Lysis Syndrome

Definition
- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, acute leukemia)

Clinical Features
- metabolic abnormalities
  - cells lyse, releasing K^+, uric acid, PO_4^{3-} (increased levels)
  - PO_4^{3-} binds Ca^{2+} (decreased Ca^{2+})
- complications
  - lethal cardiac arrhythmia (increased K^+)
  - acute kidney injury (formerly known as renal failure) see Nephrology, NP21

Treatment
- prevention
  - aggressive IV hydration
  - alkalinization not recommended due to risk of calcium phosphate or xanthine precipitation in renal tubules
  - allopurinol (prevents uric acid accumulation) or rasburicase (lowers existing uric acid)
  - correction of pre-existing metabolic abnormalities
- dialysis

Blood Products and Transfusions

Blood Products

- RBCs, platelets, and coagulation factors (FP, cryoprecipitate, fibrinogen concentrate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and plasma
  - plasma is further fractionated
    - need to pool multiple units of platelets and WBCs to obtain therapeutic amounts
    - FP (previously known as FFP) is plasma frozen within 24 h of collection
    - cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures
  - single donor platelets and plasma can also be obtained by apheresis donations

Specialized Products
- irradiated blood products
  - prevent proliferation of donor T-cells in recipients at risk of GVHD
  - used for patients with severe T-cell immunodeficiency, on purine analogue chemotherapy, with Hodgkin lymphoma, candidates for BM transplant, or receiving directed transfusions from first-degree relatives, HLA-matched products, or intrauterine transfusions
- CMV-negative blood products
  - seronegative pregnant women
  - intrauterine transfusions

Blood Groups

Group	Antigen (on RBC)	Antibody (in serum)
O	H	Anti-A, anti-B
A	A	Anti-B
B	B	Anti-A
AB	A and B	Nil

In Canada, blood products are leukodepleted via filtration immediately after donation; therefore it is considered:
- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV safe (because CMV is found in leukocytes)

Red Blood Cells

Packed Red Blood Cells
- stored at 4°C
- shelf life is 42 d after collection
- infuse each unit over 2 h (max of 4 h)

1 unit of pRBC will increase Hb by approximately 10 g/L

Indications for Packed RBC Transfusion

- Hb <70 g/L; this may change as per patient's tolerance or symptoms
  - maintain Hb between 70 and 90 g/L during active bleeds
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding

American Society of Hematology Choosing Wisely Recommendation
Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return the patient to a safe Hb range (70-80 g/L) in stable non-cardiac patients

Selection of Red Cells for Transfusion

- when anticipating an RBC transfusion, the following should be ordered:
  - group and screen: determines the blood group and Rh status of the recipient as well as the presence of auto- or alloantibodies against major/minor blood group antigens in the patient's plasma
  - cross-match: involves mixing the recipient's blood with potential donor blood and looking for agglutination (takes 30-45 min)
- when blood is required, several options are available
  - 1st-line: fully crossmatched blood, electronic crossmatch is becoming more widely used (not always available in emergency situations)
  - 2nd-line: donor blood of the same group and Rh status as the recipient
  - 3rd-line: O- blood for females of reproductive age; O +blood for all others

Platelets

Table 36. Platelet Products

Product	Indication
Random Donor (Pooled)	Thrombocytopenia with bleeding
Single Donor Platelets	Potential BMT recipients. Refractory to pooled platelets
HLA Matched Platelets	Refractory to pooled or single donor platelets, presence of HLA Abs

See Landmark Hematology Trials for more information on the FOCUS trial. It details the efficacy of liberal or restrictive transfusion in high-risk patients after hip surgery

- stored at 20-24°C
- random donor platelets come in a pool of 4 units; while a unit of apheresis platelets comes from a single donor
- 1 platelet pool should increase the platelet count by ≥15 x 10^9/L
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies (Anti-HLA or Anti-HPA), consumption (bleeding, sepsis, DIC), or hypersplenism may be present

Table 37. Indications for Platelet Transfusion

Plt (x 10^9/L)	Indications
<10	Non-immune thrombocytopenia
<20	Procedures not associated with significant blood loss
<50	Procedures associated with blood loss or major surgery (>500 mL estimated blood loss)
<100	Pre-neurosurgery or head trauma
Any	Platelet dysfunction (or antiplatelet agents) and marked bleeding

Relative Contraindications of Platelet Transfusion

- TTP, HIT, post-transfusion purpura, and HELLP

Coagulation Factors

Table 38. Coagulation Factor Products

Product	Indication
FP	Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose when factor concentrates are not available
Cryoprecipitate (enriched fibrinogen, VWF, VIII, XIII)	Hemophilia A (Factor VIII deficiency) and von Willebrand disease – use in emergencies when specific factor concentrates are not available Hypofibrinogenemia
Fibrinogen Concentrate (FC)	Hypofibrinogenemia
Humate P or Wilate	von Willebrand disease and Hemophilia A
Factor VIII concentrate	Factor VIII deficiency (Hemophilia A)
Factor IX concentrate	Factor IX deficiency (Hemophilia B)
Recombinant factor VIIa	Factor VII deficiency with bleeding/surgery, Hemophilia A or B with inhibitors, Glanzmann's thrombasthenia
Prothrombin complex concentrate; PCC (Octaplex®, Beriplex®)	Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (<6 h) surgical procedure, urgent non-specific "reversal" of direct Xa inhibitors
Activated prothrombin complex concentrate; aPCC (FEIBA)	Hemophilia A or B with inhibitors

Group & Screen vs. Cross-Matching:
G&S: ABO group + Rh factor
Cross-Matching: match recipient's serum with donor's packed RBC or Abs

Acute Blood Transfusion Reactions

DDx of Post-Transfusion Fever
Acute hemolytic transfusion reaction
Febrile non-hemolytic transfusion reaction (FNHTR)
Bacterial contamination
Allergy

DDx of Post-Transfusion Dyspnea
Transfusion-associated circulatory overload (TACO)
Transfusion-related acute lung injury (TRALI)
Allergy (bronchospasm/anaphylaxis)

IMMUNE

Acute Hemolytic Transfusion Reactions
- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation, occurs immediately after transfusion
- most commonly due to incorrect patient identification
- risk per unit of blood is <1/40000
- presentation: fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - send new specimen to blood bank for repeat testing and draw hemolysis labs: CBC, bilirubin, LDH, reticulocytes, DAT
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

Febrile Nonhemolytic Transfusion Reactions
- due to alloantibodies to WBC, platelets, or other donor plasma antigens, and release of cytokines from blood product cells
- occurs within 6 h of transfusion
- risk per unit of blood is 1/100 (minor), 1/10000 to 40000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia
- look for serious symptoms of shaking, chills/rigors, hypotension, tachycardia, anxiety, dyspnea, back/chest pain, N/V
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <39°C and no serious symptoms, continue with transfusion but decrease rate and give antipyretics
  - if temperature ≥39°C or presence of serious symptoms, stop transfusion, investigate the reaction, and start supportive measures

Allergic Nonhemolytic Transfusion Reactions
- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1/100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema, and hypotension (1/40000)
- can occur in some IgA deficient patients with anti-IgA
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenydramine, steroids, epinephrine, IV fluids, and bronchodilators

Transfusion-Related Acute Lung Injury
- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - profound hypoxemia (PaO_2/FiO_2 <300 mmHg)
  - bilateral pulmonary edema on imaging
  - no clinical evidence of left atrial hypertension or if present, judged not to be the main contributor
- pathogenesis uncertain; perhaps due to binding of donor Abs to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 h post-transfusion and resolves in 24-72 h
- risk per unit of blood is 1/10000
  - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
- inform blood bank; patient and donor testing will be arranged

NONIMMUNE

Transfusion-Associated Circulatory Overload
- due to impaired cardiac function and/or excessively rapid transfusion
- presentation: dyspnea, orthopnea, hypertension, tachycardia, crackles at base of lungs, and increased venous pressure
- incidence: 1/100
- risk factors: age >70 yr, heart failure, history of MI, renal failure, positive fluid balance
- treatment: stop transfusion, give diuretics, and oxygen. Transfuse at lower rate ± diuretics to prevent

Bacterial Infection
- Gram-positive: *S. aureus, S. epidermidis, Bacillus cereus*
- Gram-negative: *Klebsiella, Serratia, Pseudomonas, Yersinia*
- overall risk is 1/100000 for RBC and 1/10000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids

Hyperkalemia
- due to K^+ release from stored RBC
- risk increases with storage time and if blood is irradiated; decreases with fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP15

Citrate Toxicity
- occurs with massive transfusion and in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca^{2+} and causes signs and symptoms of hypocalcemia and exacerbates coagulopathy
- treatment: IV calcium gluconate 1 g

Dilutional Coagulopathy
- occurs with massive transfusion (>10 units)
- pRBC contains no coagulation factors, fibrinogen, cryoprecipitate, or platelets
- treatment: FP, cryoprecipitate, and platelets

Delayed Blood Transfusion Reactions

IMMUNE

Delayed Hemolytic
- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of Ab at time of transfusion is too low to be detected and to cause hemolysis; Ab levels increase later due to secondary stimulus and causes extravascular hemolysis
- occurs 3-14 d after transfusion
- presentation: anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion
- N.B. serologic transfusion reactions are the development of alloantibodies in the absence of frank hemolysis

Allogeneic SCT GVHD
To reduce risk of GVHD development after allogeneic SCT, administer inhibitors of T-cell activation, including cyclosporin A or tacrolimus

Transfusion-Associated Graft Versus Host Disease
- transfused T-lymphocytes recognize and react against "host" (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- presentation: fever, diarrhea, liver function abnormalities, and pancytopenia
- can be prevented by giving irradiated blood products

NONIMMUNE

Iron Overload
- due to repeated transfusions over long period of time (e.g. β-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if no longer requiring blood transfusion and not anemic

Viral Infection Risk
- HBV 1/7000000
- HCV 1/12000000
- HIV 1/20000000
- Human T-lymphotropic virus (HTLV) 1/600000000
- other infections include EBV, CMV, WNV (West Nile virus)

Common Medications

Antiplatelet Therapy

• see *Figure 12a, H27*

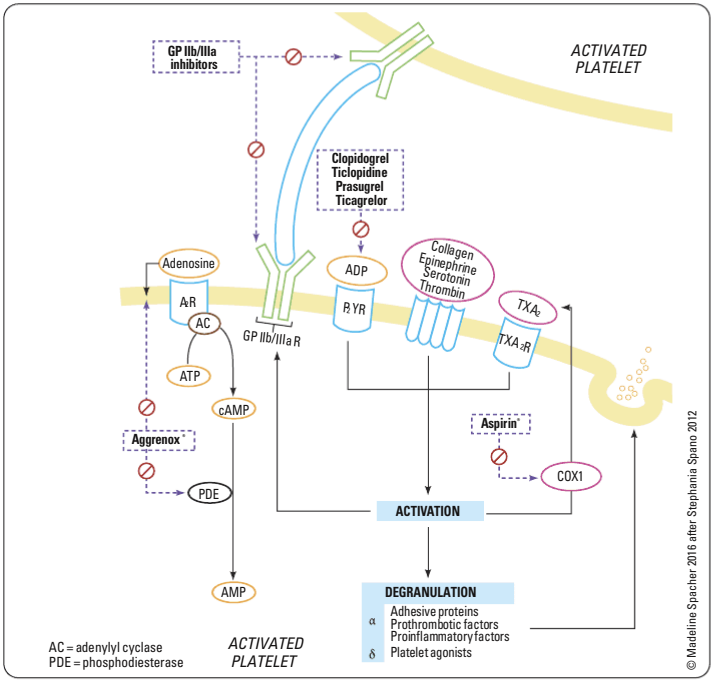

Figure 17. Mechanisms of action of antiplatelet therapy

Table 39. Antiplatelet Therapy

	Mechanism of Action	Typical Dose/ Route of Administration	Onset/Peak/ Duration	Specific Side Effects	Remarks
Aspirin® (ASA)	Irreversibly acetylates COX, inhibiting thromboxane A2 (TXA2) synthesis, thus inhibiting platelet aggregation	Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily	Onset: 5-30 min Peak: 0.25-3 h Duration: 3-6 h (platelet inhibition lasts 7-10 d)	GI ulcer/bleeding Tinnitus Bronchospasm Angioedema Reye's syndrome in pediatric patients	Indicated for stroke/MI prophylaxis Reduce incidence of recurrent MI Decrease mortality in post-MI patients Contraindicated in patients with GI ulcers
Aggrenox® (ASA + Dipyridamole)	Dipyridamole increases intracellular cAMP levels, which inhibits TXA2 synthesis, leading to decreased platelet aggregation	1 capsule PO BID	Peak: 75 min	H/A Dyspepsia N/V Abdominal pain Cardiac failure Hemorrhoids	More effective than ASA in secondary prevention of stroke Dipyridamole potentiates antiplatelet action of ASA
Clopidogrel (Plavix®)	Irreversibility inhibits ADP binding to platelets, thus decreasing platelet aggregation	Loading dose 300 mg PO, then 75 mg daily	Onset: 2 h (loading dose) Peak: 6 h (loading dose) Duration: 5 d	URI Chest pain H/A Flu-like syndrome Depression UTI GI hemorrhage Pancytopenia May cause TTP	Prevention of cardiovascular events in high-risk patients Clopidogrel is a prodrug requiring two-step activation to active metabolite CYP2C19 poor metabolizers have diminished response to clopidogrel Caution with hepatic/renal impairment
Prasugrel (Effient®)	Same as clopidogrel	Loading dose 60 mg, then 5-10 mg PO daily	Onset: 30 min (loading dose) Peak: 4 h (loading dose) Duration: 5-10 d	Dizziness H/A Nervousness Blurry vision	Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients Higher potency compared to clopidogrel No significant drug-drug interactions, although more data is required

Table 39. Antiplatelet Therapy

	Mechanism of Action	Typical Dose/ Route of Administration	Onset/Peak/ Duration	Specific Side Effects	Remarks
Ticagrelor (Brilinta®)	Reversibly inhibits ADP binding to platelets	Loading dose 180 mg, then 90 mg PO BID	Onset: 30 min (loading dose) Peak: 1.5 h for prodrug, 2.5 h for active metabolite	Difficulty or laboured breathing Shortness of breath Tightness in chest Dizziness	Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients Higher potency compared to clopidogrel Ticagrelor does not need metabolic activation to serve its antiplatelet function Drug-drug interactions with CYP3A4 inhibitors and inducers Prasugrel is a prodrug requiring metabolic activation mainly by CYP3A5 and CYP2B6
Glycoprotein IIb/IIIa Inhibitors Reopro® (abciximab), Integrilin® (eptifibatide)	Blocking GPbII/IIIa receptor inhibits fibrinogen and VWF binding, leading to decreased platelet aggregation	Variable IV	Variable	Hypotension Back pain N/V Chest pain Abdominal pain Thrombocytopenia	Used most commonly in cardiac catheterization Contraindicated in PUD Monitoring aPTT/activated clotting time

Anticoagulant Therapy

Table 40. Anticoagulant Therapy

	Mechanism of Action	Dose/Route of Administration	Onset/Peak/ Duration	Reversing Agent	Monitoring	Specific Side Effects	Remarks
Heparin	Inhibition of Factor Xa and Factor IIa, mediated via antithrombin	Variable, depends on indication; can be used IV or SC	Onset: Immediate (IV); 20-30 min (SC)	Protamine sulfate	aPTT (intrinsic pathway), UFH (anti-Xa) levels	Hemorrhage HIT Increased liver enzymes	Pregnancy: safe (does not cross placenta)
Warfarin	Vitamin K antagonist: inhibits production of Factors II, VII, IX, X, proteins C and S	Individualized dosing by monitoring PT/INR; PO	Onset: 24-72 h Peak: 5-7 d Duration: 2-5 d	Vitamin K PCC FP	INR: maintain 2-3 (2.5-3.5 for certain mechanical valves)	Hemorrhage Cholesterol embolism syndrome Intraocular hemorrhage	Pregnancy: not used, can cross placenta (teratogenic)
LMWH (enoxaparin, dalteparin, tinzaparin)	Mainly Factor Xa inhibition, some FIIa inhibition, both mediated via antithrombin	Variable, weight-based dose, depends on indication; SC/IV	Onset: 1-2 h Peak: 3-5 h Duration: 12-24 h	Partial reversibility with protamine sulfate	Anti-Xa levels in pediatrics, extremes of weight, or renal insufficiency	Hemorrhage Fever Increased liver enzymes <1% HIT	Higher bioavailability than heparin Can accumulate in patients with low CrCl (<30 mL/min) Standard treatment of VTE in pregnancy and patients with malignancy
Fondaparinux	Selective Factor Xa inhibition, mediated via antithrombin	Variable SC daily	Onset: 2 h Peak: 2-3 h	Not reversible	None	Anemia Fever Nausea Rash	Long half-life (17-21 h) Contraindicated in renal failure
Rivaroxaban	Direct Factor Xa inhibitor	Variable, depends on indication; PO	Onset: 1-3 h Peak: 1-3 h	Andexanet α	Anti-Xa levels validated for rivaroxaban may be used to detect presence of drug only	Syncope GI hemorrhage Menorrhagia Gastroentritis Cough	Indicated for treatment of acute VTE, secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl>30 mL/min; must be taken with food; contraindicated in mechanical heart valves
Apixaban	Direct Factor Xa inhibitor	PO BID	Onset: 1-3 h Peak: 1-3 h	Andexanet α	Anti-Xa levels validated for apixaban may be used to detect presence of drug only	Hemorrhage Nausea Anemia	Indicated for treatment of acute VTE, secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl >25 ml/min; contraindicated in mechanical heart valves
Edoxaban	Direct Factor Xa inhibitor	PO daily	Onset: 1-2 h Peak: 1-2 h	Andexanet α	Not typically available	Hemorrhage Rash	Indicated for treatment of acute VTE, secondary VTE prevention, stroke prophylaxis in non-valvular AFib; contraindicated in mechanical heart valves; dose reduction in renal insufficiency, avoid in CrCl <15 mL/min
Argatroban	Direct thrombin inhibitor	Variable IV	Onset: 5-10 min Duration: 20-40 min	Not reversible	aPTT	Dyspnea Hypotension Fever	Indicated for treatment of heparin-induced thrombocytopenia, PCI; contraindicated in mechanical heart valves
Dabigatran	Direct thrombin inhibitor	150 mg PO BID	Onset: 1-3 h Peak: 1-3 h	Idarucizumab	Dilute thrombin time may be used to detect presence of drug only; TT also sensitive for drug presence	GI upset Dyspepsia	Indicated for treatment of acute VTE (after 5-10 d parenteral therapy), secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl >30 mL/min; should be stored in original packaging; contraindicated in mechanical heart valves

Adverse Reactions to Heparin

- hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- HIT a hematologic emergency associated with venous or arterial thrombosis (see *Table 22, H30*)
- osteoporosis: with long-term use

Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)

- increased bioavailability compared to unfractionated heparin
- increased duration of action
- SC route of administration

- do not need to monitor aPTT
- adverse reactions less common than UFH
- patients with renal failure (CrCl <30 mL/min) can accumulate LMWH, therefore may need to adjust dose
- only partially reversible with protamine sulfate
- HIT is less common

Table 41. Recommended Management of a Supratherapeutic INR

INR	Bleeding Present	Recommended Action
>Therapeutic to 4.5	No	Lower warfarin dose or omit a dose and resume warfarin at a lower dose when INR is in therapeutic range or no dose reduction needed if INR is minimally prolonged
>4.5 to 10.0	No	Omit the next 1-2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range OR omit a dose and administer oral vitamin K 1-2.5 mg in patients with increased risk of bleeding
>10.0	No	Hold warfarin and administer oral vitamin K 2.5 to 5 mg; monitor INR more frequently and administer more vitamin K as needed; resume warfarin at a lower dose when INR is in therapeutic range
Any	Serious or life threatening	Hold warfarin and administer vitamin K 10 mg by slow IV infusion; supplement with four-factor prothrombin complex concentrate; monitor and repeat as needed

Adapted from: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;(2 suppl):e152S

Chemotherapeutic and Biologic Agents Used in Oncology

Table 42. Selected Chemotherapeutic and Biologic Agents

Class	Example	Mechanism of Action or Target
Alkylating Agent	chlorambucil, cyclophosphamide, melphalan (nitrogen mustards) carboplatin, cisplatin dacarbazine, procarbazine busulfan bendamustine	Damage DNA via alkylation of base pairs Leads to cross-linking of bases, abnormal base-pairing, DNA breakage
Antimetabolites	methotrexate (folic acid antagonist) 6-mercaptopurine, fludarabine (purine antagonist) 5-fluorouracil (5-FU) (pyrimidine antagonist) hydroxyurea cytarabine	Inhibit DNA synthesis
Antibiotics	adriamycin (anthracycline) bleomycin mitomycin C daunorubicin	Interfere with DNA and RNA synthesis
Taxanes	paclitaxel docetaxel	Stabilize microtubules against breakdown once cell division complete
Vinca-alkaloids	vinblastine vincristine vinorelbine	Inhibit microtubule assembly (mitotic spindles), blocking cell division
Topoisomerase Inhibitors	irinotecan, topotecan (topo I) etoposide (topo II)	Interfere with DNA unwinding necessary for normal replication and transcription
Steroids	prednisone dexamethasone	Immunosuppression
Purine Analogues	fludarabine cladribine	Interferes with DNA synthesis
Monoclonal Antibodies	trastuzumab (Herceptin®) bevacizumab (Avastin®) rituximab (Rituxan®), ofatumumab (Arzerra®), obinutuzumab (Gayzva®) cetuximab (Erbitux®) daratumumab	HER2 antagonist VEGF antagonist CD20 antagonist EGFR antagonist CD38 antagonist
Small Molecule Inhibitors	imatinib mesylate (Gleevec®) dasatinib nilotinib bosutinib erlotinib (Tarceva®) gefitinib (Iressa®) bortezomib (Velcade®) sunitinib (Sutent®) ibrutinib (Imbruvica®) idealasib (Zyedlig®) ruxolitinib (Jakavi®) venetoclax lenalidomide, pomalidomide	BCR-ABL inhibitor BCR-ABL inhibitor BCR-ABL inhibitor BCR-ABL inhibitor EGFR antagonist EGFR antagonist 26S proteasome inhibitor VEGFR, PDGFR antagonist BTK inhibitor P13K inhibitor JAK2 inhibitor BCR-ABL inhibitor Bcl-2 inhibitor Immunomodulators
CAR T cell therapy	tisagenlecleucel (Kymriah®) axicabtagene ciloleucel (Yescarta®)	Target CD19

Landmark Hematology Trials

Trial Name	Reference	Clinical Trial Details
Hematologic Malignancies and Related Disorders		
Long-term outcomes of imatinib treatment for chronic myeloid leukemia	NEJM 2017;376:917-927	**Title**: Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia **Purpose**: To compare the efficacy of imatinib with that of IFN-α plus low-dose cytarabine in newly diagnosed chronic-phase CML. **Methods**: 1106 patients with Ph-positive CML in the chronic phase were randomized 1:1 to imatinib or interferon α plus cytarabine. Crossover to imatinib were allowed if no response by 6 mo or major cytogenetic response by 12 mo. **Results**: Assessing the imatinib arm after a median of 11 yr of follow-upspecifically at the sixth year point, the complete cytogenetic response rate was 83%. Among patients who attained a major molecular response after 18 mo of imatinib therapy, the overall survival at 10 yr was 93% and freedom from CML-related death 100%. **Conclusions**: This 116-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.
Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. Byrd et al. 2014	NEJM 2014;371:213-23	**Title**: Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia **Purpose**: To evaluate the efficacy of ibrutinib in patients with CLL and small lymphocytic lymphoma (SLL) at risk for poor outcomes. **Methods**: 391 patients with relapsed or refractory CLL or SLL were randomly assigned to daily ibrutinib or ofatumumab. **Results**: Ibrutinib significantly improved progression-free survival (hazard ratio, 0.22; P<0.001), overall survival (0.43; P=0.005) with a higher overall response rate (42.6% vs. 4.1%, P<0.001) as compared with patients on ofatumumab. Overall survival was 90% in the ibrutinib group and 81% in the ofatumumab group at 12 mo. **Conclusion**: Ibrutinib significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL.
POLLUX	NEJM 2016;375:1319-31	**Title**: Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma **Purpose**: To assess if daratumumab lengthens PFS when added to lenalidomide and dexamethasone therapy in patients with relapsed or refractory myeloma. **Methods**: 569 patients with MM who had been previously treated were randomly assigned to either lenalidomide and dexamethasone (control group) or daratumumab plus lenalidomide and dexamethasone (daratumumab group). The primary endpoint was PFS. **Results**: PFS at 12 mo was 83.2% in the daratumumab group and 60.1% in the control group. Daratumumab had a significantly higher overall response as compared to the control group (P <0.001). Neutropenia was more frequent in the daratumumab group (51.9% vs. 37.0%). **Conclusion**: PFS was significantly lengthened by addition of daratumumab to lenalidomide and dexamethasone for patients with relapsed or refractory MM but was associated with higher rates of neutropenia.
GALLIUM	NEJM 2017;377:1331-44	**Title**: Obinutuzumab for the First-Line Treatment of Follicular Lymphoma **Purpose**: To compare rituximab-based chemotherapy with obinutuzumab-based chemotherapy in patients with untreated advanced-stage follicular lymphoma. **Methods**: 1202 patients were randomly assigned to receive induction treatment with obinutuzumab-based chemotherapy (obinutuzumab) or rituximab-based chemotherapy (rituximab). **Results**: Risk of progression, relapse, or death was significantly lower on obinutuzumab vs.rituximab (estimated 3-yr PFS, 80.0% vs. 73.3%; hazard ratio for progression, relapse, or death, 0.66; 95% CI, 0.51-0.85; P=0.001). There were more adverse events in the obinutuzumab group (grade 3-5: 74.6% vs. 67.8%; serious events: 46.1% vs. 39.9%). **Conclusion**: Obinutuzumab-based chemotherapy resulted in longer PFS than rituximab-based therapy but more frequent high-grade adverse events.
Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. Park et al. 2018	NEJM 2018;378:449-59	**Title**: Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia **Purpose**: To investigate the use of CAR-T in relapsed B-cell ALL. **Methods**: Phase 1 trial including 53 adults with relapsed B-cell ALL received an infusion of autologous T cells expressing the 19-28z CAR. **Results**: Severe cytokine release syndrome occurred in 26% of patients following infusion (95% CI, 15-40); 1 patient died. 83% of patients experienced complete remission. At median 29 mo follow-up, median overall survival was 12.9 mo (8.7-23.4) and median event-free survival was 6.1 mo (5.0-11.5). **Conclusion**: Median overall survival was 12.9 mo in the entire cohort. More adverse events occurred in patients with high disease burden.
Thrombosis		
CLOT	NEJM 2003;349:146-53	**Title**: Low-Molecular-Weight Heparin Versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer **Purpose**: To compare the efficacy of LMWH with an oral anticoagulant for preventing recurrent thrombosis in cancer patients. **Methods**: Cancer patients with acute, symptomatic proximal DVT, PE, or both were randomly assigned to dalteparin (LMWH) for 5-7 d plus a coumarin derivative for 6 mo or dalteparin alone for 6 mo. **Results**: At 6 mo, the rate of recurrent thromboembolism was 17% in the oral-anticoagulant group and 9% in the dalteparin group. Rates of major bleeding were not significantly different between groups (6% vs. 4%, respectively); any bleeding (14% vs. 19%). **Conclusions**: Dalteparin was superior to an oral anticoagulant in cancer patients for reducing recurrent thromboembolism rates without increasing bleeding risk
Influence of Preceding Length of Anticoagulant Treatment and Initial Presentation of Venous Thromboembolism on Risk of Recurrence After Stopping Treatment: Analysis of Individual Participants' Data From Seven Trials. Boutitie et al. 2011	BMJ 2011;342:d3036	**Title**: Influence of Preceding Length of Anticoagulant Treatment and Initial Presentation of Venous Thromboembolism on Risk of Recurrence After Stopping Treatment: Analysis of Individual Participants' Data From Seven Trials **Purpose**: To determine how length of anticoagulation of VTE influences recurrence risk after treatment is stopped. CAR: Individual participants' data was pooled from 7 RCTs including 2925 men or women with a first VTE who did not have cancer and had varying durations of anticoagulant treatment. **Results**: Recurrence was higher if anticoagulation was stopped at 1-1.5 mo vs. at ≥3 mo (hazard ratio 1.52, 1.14-2.02) and similar if treatment was stopped at 3 mo vs. ≥6 mo (1.19, 0.86-1.65). **Conclusion**: Risk of recurrent VTE was similar when anticoagulation was stopped after 3 mo vs. stopping after a longer course of treatment.
EINSTEIN-PE	NEJM 2012;366:1287-97	**Title**: Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism **Purpose**: To investigate the efficacy and safety of a fixed-dose rivaroxaban regimen for the treatment of PE. **Methods**: 4832 patients who had acute symptomatic PE ± DVT were randomly assigned to rivaroxaban or standard therapy with enoxaparin followed by a vitamin K antagonist. **Results**: Rivaroxaban was noninferior to standard therapy for the primary efficacy outcome (symptomatic recurrent VTE), 2.1% in rivaroxaban vs. 1.8% in standard-therapy (hazard ratio, 1.12; 95% CI, 0.75-1.68). Clinically relevant bleeding occurred in 10.3% of patients on rivaroxaban and 11.4% of those on standard-therapy (0.90; 0.76-1.07; P=0.23). **Conclusion**: For initial and long-term treatment of PE, fixed-dose rivaroxaban alone was noninferior to standard therapy with a potentially better benefit-risk profile.

Trial Name	Reference	Clinical Trial Details
AMPLIFY	NEJM 2013;369:799-808	**Title**: Oral Apixaban for the Treatment of Acute Venous Thromboembolism **Purpose**: To investigate the efficacy and safety of fixed-dose apixaban for the treatment of VTE. **Methods**: 5395 patients with acute VTE were randomly assigned to receive apixaban or conventional therapy (SC enoxaparin, followed by warfarin). **Results**: Apixaban was noninferior to conventional therapy for the primary efficacy outcome (symptomatic recurrent VTE or death from VTE) (P<0.001). Major bleeding or clinically relevant nonmajor bleeding occurred in 4.3% of patients on apixaban vs. 9.7% of those on conventional-therapy (RR, 0.44; 95% CI, 0.36-0.55; P<0.001). **Conclusion**: For the treatment of acute VTE, fixed-dose apixaban alone was noninferior to conventional therapy with significantly less bleeding.
RE-VERSE AD	NEJM 2015;373:511-20	**Title**: Idarucizumab for Dabigatran Reversal **Purpose**: To investigate the efficacy and safety of idarucizumab for reversing the anticoagulant effects of dabigatran. **Methods**: 90 patients with either a serious bleed or one requiring an urgent procedure secondary to dabigatran received idarucizumab. **Results**: Idarucizumab normalized test results in 88-98% of patients, which was evident within minutes. Unbound dabigatran concentrations remained <20 ng/mL at 24 h in 79% of patients. **Conclusion**: The anticoagulant effect of dabigatran was completely reversed by idarucizumab within minutes.
CACTUS	Lancet Haematol 2016;3:e556-e562	**Title**: Anticoagulant Therapy for Symptomatic Calf Deep Vein Thrombosis (CACTUS): A Randomised, Double-Blind, Placebo-Controlled Trial **Purpose**: To investigate the efficacy and safety of anticoagulant treatment in patients with acute symptomatic DVT of the calf. **Methods**: 259 low-risk outpatients without active cancer or previous VTE with a first acute symptomatic calf DVT were randomly assigned to receive either nadroparin (LMWH) or placebo for 6 wk. **Results**: No significant difference between groups was seen in the composite primary outcome (extension of calf DVT to proximal veins, contralateral proximal DVT, and symptomatic pulmonary embolism at day 42). Bleeding occurred in 4% of patients on nadroparin and no patients on placebo (risk difference 4.1, 95% CI 0.4-9.2; p=0.0255). **Conclusion**: In low-risk outpatients with symptomatic calf DVT, nadroparin was non-superior to placebo in reducing the risk of proximal extension or VTE, but it did increase bleeding risk.
Blood Products and Transfusion		
FOCUS	NEJM 2011;365:2453-2462	**Title**: Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery (FOCUS) **Purpose**: To determine whether a higher threshold for blood transfusion would improve recovery in patients who had undergone surgery for hip fracture. **Methods**: 2016 patients >50 yr with a history of or risk factors for cardiovascular disease and Hb level below 10 g/dL after hip-fracture surgery were randomly assigned to a liberal transfusion strategy (a Hb threshold of 10 g/dL) or a restrictive transfusion strategy (anemia symptoms or at physician discretion for a Hb level less than 8 g/dL). **Results**: The primary outcome was death or inability to walk across a room without human assistance on a 60 d follow-up. Primary outcome rates were 35.2% in the liberal transfusion strategy group and 34.7% in the restrictive transfusion strategy group. Rates of complications were similar in the two groups. **Conclusion**: A liberal transfusion strategy did not reduce mortality rates or the inability to walk independently on 60 d follow-up compared to a restrictive transfusion strategy in elderly patients with high cardiovascular risk factors after hip surgery.
TRICC BP	NEJM 1999;340:409-17	**Title**: A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group **Purpose**: To determine if equivalent results can be achieved by a restrictive strategy of red-cell transfusion and a liberal strategy in critically ill patients. **Methods**: 838 critically ill patients with euvolemia (after initial treatment and Hb <9 g/dL within 72 h of ICU admission) received either (1) a restrictive strategy (transfusion if Hb <7.0 g/dL, maintained at 7-9 g/dL) or (2) a liberal strategy (transfusions if Hb <10.0 g/dL, maintained at 10-12 g/dL). **Results**: Mortality rates at 30 d were similar between groups. However, among less acutely ill patients and those <55 yr of age, mortality rates were significantly lower in RS than LS: 8.7% vs. 16.1%, P=0.03 and 5.7% vs. 13%, P=0.02, respectively. **Conclusion**: In critically ill patients, a RS of red cell transfusion is as effective as a LS transfusion.
Therapeutic Platelet Transfusion Versus Routine Prophylactic Transfusion in Patients With Haematological Malignancies: An Open-Label, Multicentre, Randomised Study. Wandt et al. 2012	Lancet 2012;380:1309-16	**Title**: Therapeutic Platelet Transfusion Versus Routine Prophylactic Transfusion in Patients With Haematological Malignancies: An Open-Label, Multicentre, Randomised Study **Purpose**: To investigate the influence of a novel therapeutic platelet transfusion strategy on the number of transfusions and safety in patients with hypoproliferative thrombocytopenia. **Methods**: Patients (16-80 yr) undergoing chemotherapy for AML or autologous haemopoietic stem-cell transplantation were randomly assigned to receive either platelet transfusion when bleeding occurred (therapeutic strategy) or when morning platelet counts were $<10\times10^9$/L (prophylactic strategy; current standard of care). **Results**: In all patients, the therapeutic strategy reduced the mean number of platelet transfusions by 33.5% (95% CI 22.2-43.1; p<0.0001). Major haemorrhage was not increased in patients who had undergone autologous transplantation. Risk of non-fatal grade 4 bleeding was increased in patients with AML. **Conclusion**: The therapeutic strategy should be considered for patients following autologous stem-cell transplantation but not for patients with AML.
Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. Villanueva et al. 2013	NEJM 2013;368:11-21	**Title**: Transfusion Strategies for Acute Upper Gastrointestinal Bleeding **Purpose**: To compare the efficacy and safety of a restrictive transfusion strategy with a liberal transfusion strategy in patients with acute upper GI bleeds. **Methods**: 921 patients with severe acute upper GI bleeding were assigned to either a restrictive strategy (transfusion when Hb <7 g/dL; target Hb = 7-9 g/dL) or a liberal strategy (transfusion when Hb <9 g/dL; target Hb = 9-11 g/dL). **Results**: Survival at 6 wk was higher in the restrictive-strategy group than in the liberal-strategy group (95% vs. 91%; hazard ratio, 0.55; 95% CI, 0.33-0.92; P=0.02). Further bleeding was more common in patients on restrictive-strategy than liberal-strategy (10% vs.16%; P=0.01); adverse events were also more common (40% vs. 48%; P=0.02). **Conclusion**: A restrictive transfusion strategy led to better outcomes than a liberal strategy in patients with acute upper GI bleeding.

Trial Name	Reference	Clinical Trial Details
Anemia		
CHOIR	NEJM 2006;355:2085-98	**Title**: Correction of Anemia with Epoetin α in Chronic Kidney Disease **Purpose**: To determine the optimal level of hemoglobin correction by recombinant human erythropoietin (epoetin α) in anemic CKD patients. **Methods**: 1432 patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g/dL or a dose targeted to achieve a level of 11.3 g/dL. **Results**: 125 composite events (death, MI, hospitalization for CHF, or stroke) were seen in the high-hemoglobin group, as compared with 97 events in the low-hemoglobin group (hazard ratio,1.34; 95% CI, 1.03-1.74; P=0.03). **Discussion**: In patients with anemia and CKD, targeting a lower Hb reduced incidence of death, MI, CHF-related hospitalization, and stroke.
Other		
CRASH-2	Health Technol Assess 2013;17(10):1-79	**Title**: The CRASH-2 Trial: A Randomised Controlled Trial and Economic Evaluation of the Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Transfusion Requirement in Bleeding Trauma Patients **Purpose**: To assess how early administration of a short course of tranexamic acid (TXA) influences rates of death, vascular occlusive events and blood transfusions in trauma patients. **Methods**: 20211 adult trauma patients within 8 h of injury that had, or were at risk for, significant bleeding were randomized to receive TXA or matching placebo. **Results**: TXA significantly reduced all-cause mortality at 28 d (14.5% in TXA vs. 16.0% in placebo; p=0.0035). Death rates caused by bleeding were significantly reduced (4.9% vs. 5.7%; p=0.0077). The risk of death due to bleeding was increased by treatment given after 3 h (4.4% vs. 3.1%; p=0.004). **Conclusion**: The risk of death was safely reduced by early TXA in bleeding trauma patients. Beyond 3 h of injury, treatment is likely ineffective.

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ID Infectious Disease

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Acronyms

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ANC	absolute neutrophil count
AOM	acute otitis media
ARDS	acute respiratory distress syndrome
ARV	anti-retroviral
ART	anti-retroviral therapy
BAL	bronchoalveolar lavage
BCG	Bacille Calmette-Guérin
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFU	colony forming units
CLIA	ChemiLuminescent ImmunoAssay
CLL	chronic lymphocytic leukemia
CMIA	ChemiLuminescent Microparticle ImmunoAssay
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
DEET	N,N-Diethyl-meta-toluamide
DM	diabetes mellitus
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EHEC	enterohemorrhagic *E. coli*
EIA	enzyme immunoassay
EIEC	enteroinvasive *E. coli*
ETEC	enterotoxigenic *E. coli*
FDP	fibrinogen degradation products
FTA-ABS	fluorescent *Treponema* antibody-absorption
FUO	fever of unknown origin
GAS	group A *Streptococcus*
GBS	group B *Streptococcus*
GC	gonococcus
GI	gastrointestinal
GN	Gram-negative
GNB	Gram-negative bacilli
GP	Gram-positive
HAART	highly active anti-retroviral treatment
HAV	hepatitis A virus
HBc	HBV core antigen
HBeAg	HBV envelope antigen
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HHV	human herpes virus
Hib	*Haemophilus influenzae* b
HIV	human immunodeficiency virus
HPF	high power field
HPV	human papillomavirus
HRIg	human rabies immunoglobulin
HSV	herpes simplex virus
HTLV-1	Human T-lymphotropic virus 1
HUS	hemolytic uremic syndrome
IBD	inflammatory bowel disease
IDU	injecting drug use
IE	infective endocarditis
IFN	interferon
Ig	immunoglobulin
ILI	influenza-like illness
INH	isoniazid
INSTI	integrase strand transfer inhibitor
IVDU	intravenous drug use
IVIG	intravenous immunoglobulin
KOH	potassium hydroxide
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma-associated herpes virus
LDL	low-density lipoprotein
LOC	level of consciousness
LP	lumbar puncture
MERS	Middle Eastern respiratory syndrome
MDR	multidrug resistance
MHA-TP	microhemagglutination assay *T. pallidum*
MMR	measles/mumps/rubella
MRSA	methicillin-resistant S. aureus
MSM	men who have sex with men
MSSA	methicillin-sensitive S. aureus
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
O&P	ova and parasites
PCP	*Pneumocystis pneumonia*
PCR	polymerase chain reaction
PI	protease inhibitor
PJP	*Pneumocystis jirovecii* pneumonia
PMN	polymorphonuclear leukocytes
PNS	peripheral nervous system
PPD	purified protein derivative
PWID	people who inject drugs
RA	rheumatoid arthritis
mRNA	messenger ribonucleic acid
RPR	rapid plasma reagin
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcription-PCR
SARS	severe acute respiratory syndrome
SCID	severe combined immunodeficiency
SIADH	syndrome of inappropriate antidiuretic hormone secretion
Sn	sensitivity
Sp	specificity
spp.	species
SRI	severe respiratory illness
STEC	Shiga toxin-producing *E. coli*
STI	sexually transmitted infection
TB	*Mycoplasma tuberculosis*
TG	triglycerides
TIg	tetanus immune globulin
TMP/SMX	trimethoprim-sulfamethoxazole
TNF	tumour necrosis factor
TORCH	toxoplasmosis, other, rubella, cytomegalovirus, HSV
TPI	*T. pallidum* immobilization test
TPPA	*T. pallidum* particle agglutination assay
TSS	toxic shock syndrome
TST	tuberculin skin test
URTI	upper respiratory tract infection
U/S	ultrasound
UTI	urinary tract infection
VDRL	venereal disease research laboratory
VRE	vancomycin-resistant Enterococcus
VZV	varicella-zoster virus

Principles of Microbiology

Bacteriology

Bacteria Basics

- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on their cell wall
  - GP: thick, rigid layer of peptidoglycan
  - GN: thin peptidoglycan layer + outer membrane composed of lipoproteins and lipopolysaccharides
  - clinical significance: Gram stain results are used to guide tailored empiric treatment prior to availability of culture and susceptibility testing results
- acid-fast bacilli (AFB): high mycolic acid content in cell wall, called "acid fast" because they resist stain decolourization despite acid-alcohol washes (e.g. *Mycobacteria*)
- partially AFB: bacteria with moderate mycolic acid content that will decolourize with the acid alcohol used in AFB stains but are considered partially acid-fast positive based on a modified acid-fast stain with a weaker acid during the washout phase (e.g. *Nocardia*)
  - note that *Nocardia* will be acid-fast stain negative and modified acid-fast stain positive, while *Mycobacteria* will be positive on both acid-fast and modified acid-fast stains
- "atypical" bacteria: not seen on Gram stain and difficult to culture
  - obligate intracellular bacteria: e.g. *Chlamydia*
  - bacteria lacking a cell wall: e.g. *Mycoplasma*
  - spirochetes: e.g. *Treponema pallidum*
- O_2 can be either vital or detrimental to growth
  - obligate aerobes: require O_2
  - obligate anaerobes: require environment without O_2
  - facultative anaerobes: can survive in environments with or without O_2

Mechanisms of Bacterial Disease

1. adherence to and colonization of skin or mucous membranes
   - fimbriae (pili): microfilaments extending through the cell wall attach to epithelial cells (e.g. *E. coli* in the urinary tract)
2. invasion or crossing epithelial barriers
3. evasion of host defense system through:
   - inhibition of phagocytic uptake via polysaccharide capsule (e.g. *S. pneumoniae, N. meningitidis, H. influenzae*)
   - presence of surface proteins (e.g. *Staphylococcus, Streptococcus*)
4. toxin production
   - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria are not present (e.g. *Clostridium*)
   - endotoxins are structural components of GN bacterial cell walls and may be shed by live cells or released during cell lysis
5. intracellular growth
   - obligate intracellular: *Rickettsia, Chlamydia*
   - facultative intracellular: *Salmonella, Neisseria, Brucella, Mycobacteria, Listeria, Legionella*
6. biofilm
   - an extracellular polysaccharide network forming mesh around the bacteria (e.g. *S. epidermidis*) which can coat prosthetic devices such as IV catheters

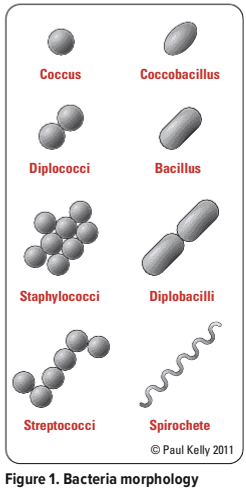


Figure 1. Bacteria morphology

Table 1. Common Bacteria

	GP Bacteria		GN Bacteria		Not Seen on Gram Stain	
	Cocci (round)	**Bacilli (rod-like)**	**Diplococci**	**Bacilli (rod-like)**	**Acid-Fast**	**Others**
Aerobes	*Staphylococcus* *S. aureus* *S. saprophyticus* *S. epidermidis* *S. lugdunensis* *Streptococcus* *S. pneumoniae* *S. pyogenes* (GAS) *S. agalactiae* (GBS) *S. anginosus group* *Enterococcus* *E. faecalis*	Bacillus *B. anthracis* *Listeria* *Nocardia* (modified acid-fast positive)	*Neisseria* *N. meningitidis* *N. gonorrhoeae* *Moraxella* *M. catarrhalis*	*Enterobacterales* *E. coli* *Klebsiella* *Salmonella* *Shigella* *Yersinia* *Campylobacter* *Legionella* *Pseudomonas* *Haemophilus* *H. influenzae*	*Mycobacteria* *M. tuberculosis* *M. leprae* *M. avium* complex	Obligate intracellular *Rickettsiae* *Chlamydia* *C. trachomatis* *C. pneumoniae* No cell wall *Mycoplasma* Spirochete (spiral) *Treponema pallidum*
Anaerobes	*Peptostreptococcus*	*Clostridioides difficile* *Clostridium* *C. tetani* *C. botulinum* *C. perfringens* *Cutibacterium (Propionibacterium) acnes*		*Bacteroides* *B. fragilis*		

Table 2. Commensal Flora

Site	Organisms
Skin	Coagulase-negative staphylococci, *Corynebacterium, C. acnes, Bacillus, S. aureus*
Oropharynx	Viridans group streptococci, *Haemophilus, Neisseria*, anaerobes (*Peptostreptococcus, Bacteroides, Veillonella, Fusobacterium, Actinomyces, Prevotella*)
Small Bowel	*E. coli*, anaerobes (low numbers)
Colon	*E. coli, Klebsiella, Enterobacter, Enterococcus*, anaerobes (*Bacteroides, Peptostreptococcus, Clostridium*)
Vagina	*Lactobacillus acidophilus*, viridans group streptococci, coagulase-negative staphylococci, facultative anaerobes

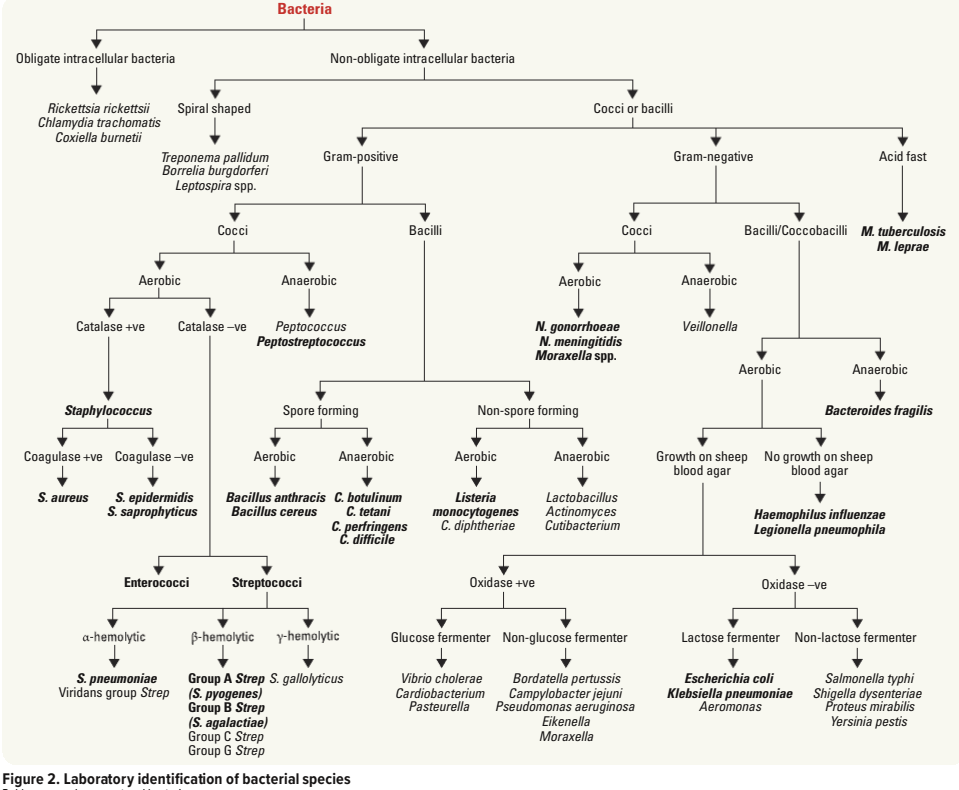


Figure 2. Laboratory identification of bacterial species
Bold = commonly encountered bacteria

Virology

Viral Basics

- viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - infect cells and use host metabolic machinery to replicate
  - nucleic acid can be double stranded (ds) or single stranded (ss)
  - nucleic acid can be positive sense (+) or negative sense (-)
  - can be enveloped or naked
- virions are mature virus particles that can be released into the extracellular environment
- host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

Viral Disease Patterns

1. acute infections (e.g. adenovirus)
   - host cells are lysed in the process of virion release
   - some produce acute infections with late sequelae (e.g. measles virus-induced subacute sclerosing panencephalitis)
2. chronic infections (>6 mo) (e.g. HBV, HIV)
   - host cell machinery is used to produce and chronically release virions
3. latent infections
   - viral genome remains latent in host cell nucleus
   - can reactivate (e.g. HSV, VZV)

Table 3. Common Viruses

Nucleic Acid	Enveloped	Virus Family	Major Viruses	Medical Importance
dsDNA	No	Adenoviridae	Adenovirus	URTI Conjunctivitis Gastroenteritis
	No	Papillomaviridae	HPV1,4 HPV6,11 HPV16,18, etc.	Plantar warts Genital warts Cervical/anal dysplasia and cancer
	Yes	Herpesviridae	HHV1=HSV1 HHV2=HSV2 HHV3=VZV HHV4=EBV HHV5=CMV HHV6* HHV8=KSHV	Oral, ocular, and genital herpes; encephalitis Genital, oral, and ocular herpes; encephalitis Chicken pox, shingles Mononucleosis, viral hepatitis Retinitis, pneumonitis, hepatitis, encephalitis Roseola Kaposi's sarcoma, multicentric Castleman's disease, body cavity lymphoma
	No	Polyomaviridae	JC virus	Progressive multifocal leukoencephalopathy
	Yes	Hepadnaviridae	Hepatitis B	Hepatitis
	Yes	Poxviridae	Monkeypox Smallpox	Monkeypox Smallpox
ssDNA	No	Parvoviridae	Parvovirus B19	Erythema infectiosum (Fifth disease)
(+) ssRNA	No	Caliciviridae	Noroviruses Hepatitis E	Gastroenteritis Acute hepatitis
	No	Picornaviridae	Poliovirus Echovirus Rhinovirus Coxsackie virus Hepatitis A	Poliomyelitis URTIs, viral meningitis URTIs Hand-foot-and-mouth, viral meningitis, myocarditis Acute hepatitis
	Yes	Coronaviridae	Coronavirus	URTIs, SARS, MERS, COVID-19
	Yes	Flaviviridae	Yellow fever Dengue fever Hepatitis C West Nile Zika	Yellow fever Dengue fever Hepatitis Encephalitis, flaccid paralysis Zika virus disease
	Yes	Togaviridae	Rubella Chikungunya	Rubella (German measles) Chikungunya
(+) ssRNA-RT	Yes	Retroviridae	HIV HTLV-1	AIDS T-cell leukemia and lymphoma
(-) ssRNA	Yes	Arenaviridae	Lassa	Lassa fever
	Yes	Filoviridae	Ebola, Marburg	Hemorrhagic fever
	Yes	Orthomyxoviridae	Influenza A, B, C	Influenza
	Yes	Paramyxoviridae	Measles Mumps Parainfluenza RSV	Measles Mumps URTIs, croup, bronchiolitis Bronchiolitis, pneumonia
	Yes	Rhabdoviridae	Rabies	Rabies
dsRNA	No	Reoviridae	Rotavirus	Gastroenteritis

Note: ___viridae = family, ___virus = genus, # = species (e.g. Retroviridae HIV-2)
*Roseolovirus, Herpes lymphotropic virus

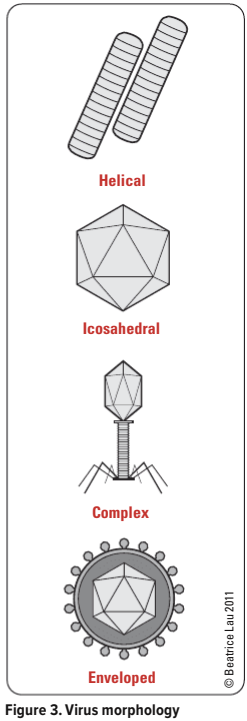


Figure 3. Virus morphology

DNA Viruses: Families

HHAPPPPy
Hepadnaviridae
Herpesviridae
Adenoviridae
Papillomaviridae
Parvoviridae
Polyomaviridae
Poxviridae

Mycology

Fungal Basics

- fungi are eukaryotic organisms, they can have the following morphologies
  1. yeast (unicellular)
  2. moulds, i.e. filamentous fungi (multicellular with hyphae)
  3. dimorphic fungi (found as mould at room temperature but grow as yeast-like forms at body temperature)

Table 4. Membrane and Cell Wall Compositions

	Membrane Sterol	Cell Wall
Bacteria	–	Peptidoglycan
Human Cell	Cholesterol	–
Fungi	Ergosterol	Chitin (complex glycopolysaccharide)

Mechanisms of Fungal Disease

- primary fungal infection by:
  - overgrowth of normal flora (e.g. *Candida* spp.)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion of aflatoxins)
- allergic reactions to fungi (e.g. bronchopulmonary aspergillosis)

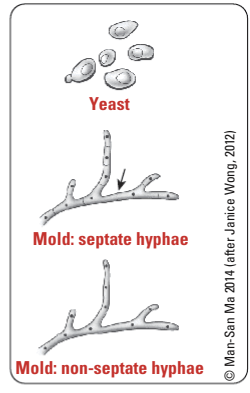


Figure 4. Common fungus morphology

Parasitology

Parasite Basics

- parasite: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycles require more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed through the larval stages
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see *Table 25, ID33* and *Table 26, ID39* for examples of clinically important parasites

Table 5. Differences Between Protozoa and Helminths

Protozoa	Helminths
Unicellular	Multicellular
Motile trophozoite, inactive cyst	Adult → egg → larva
Multiplication	No multiplication in human host
Eosinophilia unusual	Eosinophilia (proportional to extent of tissue invasion)*
Indefinite life span	Definite life span

*Adult *Ascaris* (roundworm) does not cause eosinophilia; migratory larval phases of *Ascaris*, however, cause high-grade eosinophilia

Characteristics of Parasitic Disease

- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic worm infection

Mechanisms of Parasitic Disease

1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B_{12} deficiency in diphyllobothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
   - acute hypersensitivity (e.g. pneumonitis in Loeffler's syndrome)
   - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
   - cytokine-mediated (e.g. systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
   - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
   - immune complex (e.g. nephritis of malaria, schistosomiasis)

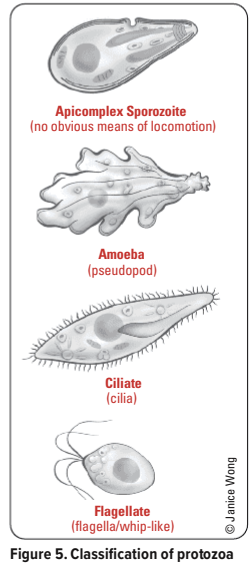


Figure 5. Classification of protozoa based on movement

Parasite sampling may need to be repeated on several occasions before infection can be ruled out

Transmission of Infectious Diseases

Table 6. Mechanism of Transmission

Mechanism	Mode of Transmission	Examples	Preventative Measure
Contact	Direct physical contact, or indirect contact with a fomite	Skin-to-skin (MRSA) Sexual (*N. gonorrhoeae, C. trachomatis*, HSV, HIV) Blood-borne (HIV, HBV, HCV)	For patients in healthcare facilities: Contact precautions Barrier precautions Safe needlestick/sharp practices
Droplet/Contact	Respiratory droplets (>5 µm) can be projected short distances (≤2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids	Influenza, mumps, *N. meningitidis, Bordetella pertussis*	For patients in healthcare facilities: Contact/droplet precautions
Airborne	Airborne droplet nuclei (<5 µm) remain infectious over time and distance	*M. tuberculosis*, disseminated VZV, measles	For patients in healthcare facilities: Airborne precautions
Food/ Waterborne	Ingestion of contaminated food or water	*V. cholerae, Salmonella*, HAV, HEV	Prophylactic vaccinations where available Ensure clean food/water supply For patients in healthcare facilities: Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers
Zoonotic/Vector-borne	Disease transmission from animals to humans either directly or via an insect vector, or disease transmission from human to human via an insect vector	Direct animal transmission (rabies, Q fever) Arthropod mediated transmission (malaria, Lyme disease, West Nile virus)	Prophylactic medications, vaccinations Prophylactic medications, vaccinations Protective clothing, insect repellent, mosquito nets, tick inspection
Vertical	Spread of disease from parent to offspring	Congenital syndromes (TORCH infections) Perinatal (HIV, HBV, GBS)	Prenatal screening Prophylactic treatment

Nosocomial Infections

- **definition**: infections acquired >48 h after admission to a healthcare facility OR within 30 d from discharge
- **risk factors**: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, and immunodeficiency
  - patients with nosocomial infections have higher mortality, longer hospital stays, and higher healthcare costs
- hand hygiene is an essential precaution

Table 7. Common Nosocomial Infectious Agents

Bacteria	Characteristics	Manifestation	Investigations	Management
MRSA	GP cocci	Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis	Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR	Contact precautions For infection: vancomycin, daptomycin, or linezolid To decolonize: chlorhexidine 2% wash once daily (+ rifampin + (doxycycline or TMP/SMX) + mupirocin cream BID to nares) x 7 d
VRE	Majority are *E. faecium* Resistant if minimum inhibitory concentration of vancomycin is ≥32 µg/mL	Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis	Rectal or perirectal swab OR stool culture for colonization Culture of infected site	Contact precautions* Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified
***Clostridioides difficile* (*C. difficile*)**	Releases exotoxins A and B Hypervirulent strain (NAP1/B1/027) has been responsible for increase in incidence and severity	Fever, nausea, abdominal pain Watery diarrhea Pseudomembranous colitis Severe: toxic megacolon Risk of bowel perforation Associated with antibiotic use Leukocytosis	Stool PCR for toxin A and B genes Stool immunoassay for toxins A and B (less sensitive than PCR) Abdominal x-ray (may see colonic dilatation) Sigmoidoscopy for pseudomembranes; avoid if known colonic dilatation	Contact precautions Stop culprit antibiotic therapy (primarily fluoroquinolones and clindamycin) Supportive therapy (IV fluids) Empiric treatment with either vancomycin or fidaxomicin If access to empiric treatment is limited, then metronidazole may be used For fulminant *C. difficile* infection (previously called severe), oral vancomycin is used. IV metronidazole added to regimen if ileus present
Extended Spectrum β-lactam Producers (e.g. ESBL producing *E. coli, K. pneumoniae*)	Resistant to most β-lactam antibiotics except carbapenems e.g. penicillins, aztreonam**, and cephalosporins	UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis	Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)	Contact precautions* Carbapenems or non-β-lactam antibiotics can be used for empiric therapy
Carbapenemase-producing Enterobacterales (CPE)	Resistant to β-lactam antibiotics including carbapenems	UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis	Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)	Contact precautions Colistin, tigecycline can be used varying on susceptibility Cefiderocol, ceftazidime-avibactam, or plazomicin are other options available through the Special Access Program

*The use of contact precautions for VRE and ESBL varies depending on institutional policies. **Not available in Canada

Respiratory Infections

Pneumonia

- see Pediatrics, P68

Definition

- infection of the lung parenchyma

Etiology and Risk Factors

- impaired lung defenses
  - poor cough/gag reflex (e.g. illness, drug-induced)
  - impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  - immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
- increased risk of aspiration
  - impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia)
- mechanical obstruction
- no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

Table 8. Common Organisms in Pneumonia

Community-Acquired	Nosocomial	Aspiration	Immunocompromised Patients	Alcohol Use Disorder
Typical Bacteria *Streptococcus pneumoniae* *Moraxella catarrhalis* *Haemophilus influenzae* *Staphylococcus aureus* GAS Atypical Bacteria *Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Legionella pneumophila* Viral *Influenza virus* *Adenovirus* *SARS-CoV-2*	Enteric GNB (e.g. *E. coli*) *Pseudomonas aeruginosa* *S. aureus* (including MRSA)	Oral anaerobes (e.g. *Bacteroides*) Enteric GNB *S. aureus* Gastric contents (chemical pneumonitis)	*Pneumocystis jirovecii* Fungi (e.g. *Cryptococcus*) *Nocardia* CMV HSV TB	*Klebsiella* Enteric GNB *S. aureus* Oral anaerobes (aspiration) TB

*See Pediatrics, P87, Table 45, *Common Causes and Treatment of Community-Acquired Pneumonia*

Clinical Features

- cough (± sputum), fever, pleuritic chest pain, dyspnea, tachypnea, and tachycardia
- elderly often present atypically; altered LOC is sometimes the only sign
- evidence of consolidation (dullness to percussion, bronchial breath sounds, and crackles)
- features of parapneumonic effusion (decreased air entry, dullness to percussion)
- complications: ARDS, lung abscess, parapneumonic effusion/empyema, and pleuritis ± hemorrhage

Investigations

- pulse oximetry to assess severity of respiratory distress
- CBC and differential, electrolytes, urea, creatinine, arterial blood gas (ABG) (if respiratory distress)
- sputum Gram stain/C&S, blood C&S, ± viral detection (influenza testing), ± serology, and ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
- CXR ± CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
- bronchoscopy ± washings for: (1) severely ill patients refractory to treatment and (2) immunocompromised patients

Treatment

- airway/breathing/circulation, O_2, IV fluids, consider salbutamol (nebulized or metered-dose inhaler)
- determine prognosis and need for hospitalization and antibiotics

Criteria for Hospitalization

- along with clinical judgment, validated clinical prediction rules for prognosis can be used to determine the need for hospitalizations in adults diagnosed with community-acquired pneumonia (e.g. the CURB-65 Score or Pneumonia Severity Index (PSI))

Table 9. CURB-65 Score – Pneumonia Clinical Prediction Tool

Component*	Measurement(s)	Points	Total Score	Mortality	Disposition
Confusion	Altered mental status	1	0-1	<5%	Can treat as outpatient
Urea/BUN	Urea >7 mmol/L or BUN >20 mg/dL	1	2-3	5-15%	Consider hospitalization
Respiratory Rate	>30 breaths/min	1	4-5	15-30%	Consider ICU
Blood Pressure	sBP <90 mmHg or dBP <60 mmHg	1			
Age	65 or older	1			

*A CRB-65 score may also be applied in community acquired pneumonia. Its criteria depends on clinical assessment alone

When Klebsiella causes pneumonia: see red currant jelly sputum

3 As of *Klebsiella*
Aspiration pneumonia
Alcohol use disorder and patients with diabetes
Abscess in lungs

Aspiration pneumonias more commonly manifest as infiltrates in the right middle or lower lobes due to the larger calibre and more vertical orientation of the right bronchus

Healthcare-Associated Infections and Antimicrobial Resistance in Canadian Acute Care Hospitals
Can Commun Dis Rep 2020;46:99-112
Purpose: To describe the trends of healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) from 2014 to 2018 using surveillance data from the Canadian Nosocomial Infection Surveillance Program.
Methods: Data were collected from 70 Canadian sentinel hospitals regarding Clostridioides difficile infection (CDI), MRSA bloodstream infections, VRE bloodstream infections, and carbapenemase-producing Enterobacteriaceae.
Results: Rates per 10,000 patient-days increased for MRSA (59%; 0.66-1.05, P=0.023) and VRE bloodstream infections (143%; 0.14-0.34, P=0.023). However, CDI rates decreased by 12.5% (from 6.16-5.39, P=0.042). Carbapenemase-producing Enterobacteriaceae colonization increased by 375% (0.04-0.19; P=0.014) but infection rates remained low and stable.
Conclusion: Standardized surveillance data from acute care hospitals in addition to antimicrobial stewardship will be crucial for the ongoing prevention of HAIs and AMR in Canada.

For a report on nosocomial infections in the US, please refer to: NEJM 2014;370:1198-208. Consult your local hospital statistics for the most applicable information for your workplace.

Diagnosis of Ventilator-Associated Pneumonia in Critically Ill Adult Patients: A Systematic Review and Meta-Analysis
Intensive Care Med 2020;46:1170-79
Purpose: To identify and compare the accuracy of the following measures for diagnosing VAP: physical examination, chest radiography, endotracheal aspirate (ETA), bronchoscopic sampling cultures (protected specimen brush (PSB) and bronchoalveolar lavage (BAL)), and CPIS >6.
Study Selection: Eligible observational studies and RCTs included ≥90% patients over 16 y/o with measures conducted in the ICU, including patients with minimum 48 h of invasive mechanical ventilation.
Results: The collective sensitivity and specificity of VAP physical examination findings were poor: fever (66.4% and 53.9%, respectively) and purulent secretions (77.0%, 39.0%); any infiltrate on chest radiography (88.9%, 26.1%); ETA (75.7%, 67.9%). Among bronchoscopic sampling methods, PSB (61.4%, 76.5%); BAL (71.1%, 79.6%). CPIS>6 (73.8%, 66.4%).
Conclusion: VAP misdiagnosis and potentially unnecessary antimicrobial use may result from reliance on classical clinical measures used in isolation.

Table 10. Pneumonia Severity Index – Clinical Prediction Rule for Prognosis

Risk Factor	Points	Total Score	Risk Class	Mortality	Recommendation
Demographics		<51	I	0.1%	Consider outpatient
Men	Age (yr)				
Women	Age (yr) – 10				
Nursing home resident	+10				
Coexisting Illness		51-70	II	0.6%	Consider outpatient
Neoplastic disease	+30				
Liver disease	+20				
Congestive heart failure	+10				
Cerebrovascular disease	+10				
Renal disease	+10				
Physical Exam		71-90	III	0.9-2.8%	Consider outpatient
Altered mental status	+20				
Respiratory rate ≥30 breaths/min	+20				
sBP <90 mmHg	+20				
T <35°C or ≥40°C	+15				
HR ≥125 bpm	+10				
Investigations		91-130	IV	8.2-9.3%	Hospitalize
Arterial pH <7.35	+30				
BUN ≥30 mg/dL	+20				
Sodium <130 mmol/L	+20	>130	V	27.0-29.2%	Hospitalize
Glucose ≥250 mg/dL	+10				
Hematocrit <30%	+10				
Partial pressure of arterial O_2 <60 mmHg	+10				
Pleural effusion	+10				

Adapted with permission from Diagnosis and Treatment of Community-Acquired Pneumonia, February 1, 2006, Vol 73, No 3, American Family Physician Copyright © 2006 American Academy of Family Physicians. All Rights Reserved

Table 11. IDSA/ATS Community-Acquired Pneumonia Treatment Guidelines 2019

Setting	Circumstances	Treatment
Outpatient	No comorbidities or risk factors for MRSA or *P. aeruginosa* [1]	Amoxicillin OR Doxycycline OR Macrolide (local pneumococcal resistance <25%)[2]
	Comorbidities [3]	Amoxicillin/clavulanate or cephalosporin[4] AND Macrolide[2] or doxycycline OR Respiratory fluoroquinolone[5]
Inpatient	Nonsevere inpatient pneumonia[6] and no risk factors for MRSA or *P. aeruginosa*[1]	β-lactam[7] ± macrolide [2] OR respiratory fluoroquinolone[5]
	Severe inpatient pneumonia[6] and no risk factors for MRSA or *P. aeruginosa*[1]	β-lactam[7]+ macrolide [2]OR β-lactam[7]+ fluoroquinolone [5]

Given different regional resistance patterns, therapy should be based on local epidemiology and site-specific recommendations
Refers to empiric treatment to be started. Appropriate antibiotic therapy should be tailored if pathogen is identified
1. Previous respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND parenteral antibiotic use in last 3 mo ± locally validated risk factors
2. **Macrolide:** use azithromycin or clarithromycin
3. **Comorbidities:** chronic heart, lung, liver, or renal disease, DM, alcohol use disorder, malignancy, asplenia
4. **Cephalosporin:** cefpodoxime or cefuroxime
5. **Respiratory fluoroquinolone:** moxifloxacin, levofloxacin
6. Severe = 1 major criterion or ≥3 minor criteria. Minor criteria: respiratory rate ≥30 breaths/min, PaO_2/FiO_2 ratio ≤250, multilobar infiltrates, confusion/disorientation, BUN ≥20 mg/dL, WBC <4000/μL due to infection, Plt <100000/μL, T <36°C, hypotension with aggressive fluid resuscitation. Major criteria: septic shock with vasopressors, respiratory failure with mechanical ventilation
7. **β-lactam:** ampicillin sulbactam*, cefotaxime, ceftriaxone, ceftaroline*
IDSA: Infectious Diseases Society of America
ATS: American Thoracic Society
*Available in Canada through the Special Access Program

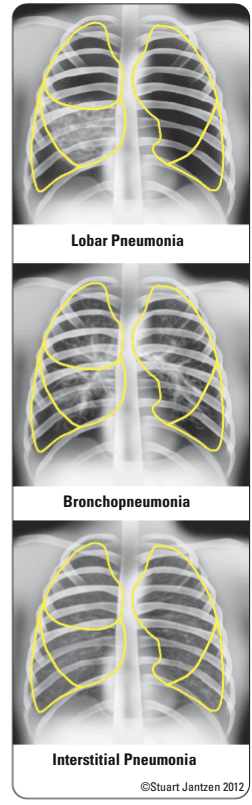


Figure 6. Lobar, broncho-, and interstitial pneumonia

Diagnosis and Treatment of Adults with Community-Acquired Pneumonia: An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America
Am J Respir Crit Care Med 2019;200:e45-e67

- The Pneumonia Severity Index is preferred over the CURB-65 tool for determining inpatient vs. outpatient treatment.
- Test for influenza with a rapid influenza molecular assay when it is circulating in the community.
- Obtaining blood C&S or sputum Gram stain/C&S routinely in adults with CAP managed in the outpatient setting is not recommended.
- Obtaining pre-treatment blood C&S and sputum Gram stain/C&S is recommended in adults with CAP managed in the hospital setting who (1) are classified as severe CAP or (2) are being empirically treated for MRSA or P. aeruginosa or (3) were previously infected with MRSA or P. aeruginosa or (4) were hospitalized and received parenteral antibiotics in the last 90 d.

Table 12. IDSA/ATS Hospital-Acquired (HAP) and Ventilator-Associated (VAP) Pneumonia Clinical Practice Guidelines 2016

Setting	Treatment
Clinically suspected **HAP** (non-VAP) with no increase in likelihood of MRSA and not at high-risk of mortality	**One of:** piperacillin-tazobactam OR cefepime OR levofloxacin OR imipenem OR meropenem
Clinically suspected **HAP** (non-VAP) with increasing likelihood of MRSA and not at high-risk of mortality	**One of:** piperacillin-tazobactam OR cefepime or ceftazidime OR levofloxacin or ciprofloxacin OR imipenem or meropenem OR aztreonam* **PLUS one of:** vancomycin or linezolid for MRSA coverage
Clinically suspected **HAP** (non-VAP) with high-risk of mortality or recipient of IV antibiotics in last 90 d	**Two of the following (avoid 2 β-lactams):** piperacillin-tazobactam OR cefepime or ceftazidime OR levofloxacin or ciprofloxacin OR imipenem or meropenem OR aztreonam* OR amikacin or gentamicin or tobramycin **PLUS either MRSA or MSSA coverage:** **MRSA**: vancomycin or linezolid OR **MSSA**: piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem
Clinically suspected **VAP** in units where empiric **MRSA** coverage and double antipseudomonal/**GN** coverage are appropriate	**One of:** β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) OR antipseudomonal cephalosporin (cefepime or ceftazidime) OR antipseudomonal carbapenem (imipenem or meropenem) OR monobactam (aztreonam*) **PLUS one of:** antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside (amikacin, gentamicin, or tobramycin) OR polymyxins (colistin or polymyxin B) **PLUS one of:** vancomycin or linezolid for MRSA coverage

Refers to empiric treatment to be started. Appropriate antibiotic therapy should be tailored if pathogen is identified
***Available in Canada through the Special Access Program**
Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock
Risk factors for MDR VAP: prior IV antibiotic use within 90 d, septic shock at time of VAP, ARDS preceding VAP, 5+ d of hospitalization prior to VAP onset, acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP, MRSA VAP/HAP, or MDR *Pseudomonas* VAP/HAP: Prior IV antibiotic use within 90 d
Note: Indications for MRSA coverage includes IV antibiotic treatment during the prior 90 d and treatment in a unit where prevalence of MRSA of *S. aureus* isolates is not known or is >20%
Note: These guidelines may be less applicable in Canada given lower rates of antibiotic resistance among common nosocomial pathogens

Prevention

- Public Health Agency of Canada recommends the following:
  - vaccine for influenza A and B annually for all ages ≥6 mo
  - pneumococcal polysaccharide vaccine (Pneumovax®) for all adults ≥65 yr and in younger patients ≥24 mo at high-risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia, congenital or acquired immunodeficiency)
  - pneumococcal conjugate vaccine (Prevnar-13®) for children and adolescents ages 5-17 yr at high risk for invasive pneumococcal disease and who have not previously received Prevnar-13® (CDC recommends giving Prevnar-13® to all adults at high-risk for invasive pneumococcal disease)
  - mRNA COVID-19 vaccine (Moderna (Spikevax®) or Pfizer-BioNTech (Comirnaty®)) for all ages ≥6 mo who do not have contraindications, with boosters as per public health guidance

Influenza

Definitions and Etiology

- influenza viruses A and B
- influenza A further divided into subtypes based on envelope glycoproteins
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: influenza A (H1N1), influenza A (H3N2), and influenza B
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift: abrupt, major changes due to mixing of two different viral strains from different hosts
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

Does this Patient have Community-Acquired Pneumonia?
Diagnosing Pneumonia by History and Physical Examination
JAMA 1997;278:1440-1445
Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult community-acquired pneumonia.
Results: The presence of fever or immunosuppression had a positive likelihood ratio (+LR) of 2, while a history of dementia had a +LR of 3; however, these traits are not confirmatory. The presence of an abnormality in any vital sign, including tachycardia, tachypnea, or fever had a +LR ranging from 2-4, which was not significantly affected by different cut-points. The absence of vital sign abnormality had a –LR ranging from 0.5-0.8. The combination of respiratory rate <30 breaths/min, heart rate <100 bpm, and temperature <37.8°C had a –LR of 0.18. Findings on chest exam raised the likelihood of diagnosis but were uncommonly seen in studies (e.g. presence of asymmetric respirations essentially confirmed the diagnosis but was only present in 4% of patients). In patients with a clinical diagnosis but normal radiograph, only ~10% will develop radiographic findings in 72 h.
Conclusions: Evidence suggests no single item on clinical history or physical exam is sufficient to rule in or out pneumonia without CXR. Vital sign abnormalities were correlated with a diagnosis of pneumonia. Findings on chest exam significantly raised the likelihood of pneumonia but were uncommonly seen in studies.

Beware! Do Not Confuse *H. influenzae* with Influenza Virus
H. influenzae: a bacterium (Types A, B, C, D, E, and F refer to capsule)
Influenza: a virus (Types A and B refer to strain)

Vaccines for Preventing Influenza in Healthy Adults
Cochrane DB Syst Rev 2018;CD001269
Study: 52 RCTs and quasi-RCTs evaluating influenza vaccines compared to placebo or no intervention in healthy individuals 16-65 yr. Observational comparative studies were not included.
Results: Inactivated influenza vaccines reduce influenza in healthy adults from 2.3% to 0.9% and reduce influenza-like illness (ILI) from 21.5% to 18.1%. The preventative effect of vaccination is small, with 71 healthy adults needing to be vaccinated to prevent one from experiencing influenza, and 29 needing to be vaccinated to prevent one from experiencing ILI. Vaccination leads to a small reduction in the risk of hospitalization from 14.7% to 14.1%, and a small reduction in days off work. Effectiveness of the influenza vaccine is less in mothers and newborns compared to the general population.
Conclusions: Influenza vaccines have a very modest effect in reducing influenza, associated symptoms, hospitalization, and days off work in healthy adults.

Table 13. Difference Between Influenza Strains

	Influenza A	Influenza B
Host(s)	Humans, birds, mammals	Humans only
Antigenic Drift	Yes, new strains	Yes, new strains
Antigenic Shift	Yes, new subtypes	No
Epidemics	Yes	Yes
Pandemics	Yes	No

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection
NEJM 2018;378:345-353
Purpose: To investigate the association between laboratory-confirmed influenza infection and acute MI.
Methods: Self-controlled case-series. Risk interval defined as first 7 d after respiratory specimen collection and control interval as 1 yr before and 1 yr after the risk interval.
Results: Increased incidence ratio of an admission for acute MI during risk interval vs. control interval (6.05, 95% CI 3.86-9.50). No increased incidence after 7 d. Increased incidence ratios for acute MI within 7 d after detection of influenza B (10.11, 95% CI 4.37-23.38), influenza A (5.17, 95% CI 3.02-8.84), and respiratory syncytial virus (3.51, 95% CI 1.11-11.12).
Conclusions: Significant association between respiratory infections, especially influenza, and acute MI.

Clinical Features
- incubation period 1-4 d and symptoms typically resolve in 7-10 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, headache, and fatigue) and respiratory symptoms (cough, dyspnea, and pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, and sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, and Guillain-Barré syndrome)
- severe disease more likely in the elderly, children, pregnant women, immunocompromised patients, asthma, COPD, cardiovascular disease (CVD), DM, and obesity

Investigations
- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for RT-PCR (gold standard), or rapid antigen detection (DFA, direct fluorescent antibody) which has lower sensitivity
- lower respiratory specimens for RT-PCR
- serology: rarely used for clinical management

Treatment and Prevention
- primarily supportive unless severe infection or high-risk for complications
- neuraminidase inhibitors: oseltamivir (Tamiflu®) or zanamivir (Relenza®) for treatment and prophylaxis against types A and B or peramivir (Rapivab™) for the treatment against types A and B
  - decreases duration (by ~1 d) and severity of symptoms if given within 48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- vaccine for influenza A and B viruses is recommended annually for all ages ≥6 mo
- vaccine is reformulated each year to reflect circulating influenza A and B strains

High-risk for Complications
- anyone who is hospitalized, patients with severe illness/chronic medical conditions, immunocompromised patients, children <2 yr, elders ≥65 yr, pregnant women or women ≤2 wk postpartum

COVID-19

Definitions and Etiology
- an acute infectious respiratory disease caused by the SARS-CoV-2 virus
- SARS-CoV-2 is an enveloped, positive-sense, ssRNA virus
- transmission: droplet and airborne transmission
- incubation period 2-14 d, usually ~5 d

Pathophysiology
- invasion of host cells via the viral spike protein which binds to angiotensin-converting enzyme 2 (ACE2) expressed on the surface epithelium of the lungs
- virus induced cytotoxic damage particularly to the alveolar epithelium
- dysregulated immune response can lead to a cytokine storm causing organ failure or death

Clinical Features
- can be asymptomatic (estimated to be 1 in 3 of those infected)
  - children are more likely to be asymptomatic or to have mild disease
- most common: fever, fatigue, and dry cough
- common: dyspnea, loss of smell and/or taste (may vary depending on the variant circulating), loss of appetite, and myalgia
- less common: nausea, vomiting, abdominal pain, sore throat, headache, and thromboembolic events
- course: can range from mild disease (lasts 1-2 wk) to severe or critical disease (lasts 3+ wk); may be complicated by post-COVID condition which is associated with a wide range of diverse symptoms across multiple organ systems that may fluctuate in intensity, often exacerbated by mental and physical overexertion

Diagnosis
- nasopharyngeal swabs for RT-PCR (gold standard) or nasal/oral-nasal swabs for rapid antigen detection point of care tests which have lower sensitivity
- lower respiratory specimens for RT-PCR

Treatment (accurate as of July 2023)
- please see updated guidance through the Ontario Science Table (https://covid19-sciencetable.ca/science-briefs/#infectious-diseases-clinical-care)

- for critically ill adults >18 yr requiring ventilatory and/or circulatory support:
  - dexamethasone PO or IV for 10 d (or until discharge)
  - tocilizumab if on recommended steroid dose + admitted to hospital or diagnosed with COVID-19 in hospital within 14 d
  - prophylactic low molecular-weight or unfractionated heparin
- for adults >18 yr requiring low-flow supplemental O_2:
  - dexamethasone PO or IV for 10 d (or until discharge)
  - remdesivir IV for 5 d
  - tocilizumab if serum CRP ≥ 75 mg/L + disease progression despite 24-48 h of recommended steroid dose + admitted to hospital or diagnosed with COVID-19 in hospital within 14 d
  - prophylactic low molecular-weight or unfractionated heparin
- for mildly ill adults >18 yr who do not require supplemental O_2 in any setting:
  - stratify by risk of severe disease (i.e. ≥5% risk of hospitalization)
  - for patients with ≥5% risk of hospitalization:
    - nirmatrelvir/ritonavir (Paxlovid) if presenting within 5 d of symptom onset
    - remdesivir if presenting within 7 d of symptom onset
- for patients with <5% risk of hospitalization: reassurance and self-monitoring of symptoms

Table 14. Risk of Hospitalization in Mildly Ill Adults >18 yr with COVID-19 (accurate as of April 1, 2022)

- Higher risk individuals are those who have a ≥5% risk of hospitalization if they develop COVID-19. Standard risk individuals are those who have a <5% of hospitalization.
- Indigenous people, Black people, and members of other racialized communities may be at increased risk of disease progression due to disparate rates of comorbidity, increased barriers to vaccination, and social determinants of health. They should be considered priority populations for access to COVID-19 drugs and therapeutics.

Age (Years)	Number of Vaccine Doses			Risk Factors
	0 Doses	**1 or 2 Doses**	**3 Doses**	Obesity (BMI ≥30 kg/m^2)
<20[1]	**Higher risk** if ≥3 risk factors [1]	Standard risk [1]	Standard risk [1]	Diabetes
20 to 39	**Higher risk** if ≥3 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	Heart disease, hypertension, congestive heart failure
40 to 69	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	Chronic respiratory disease, including cystic fibrosis
≥70	**Higher risk**	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	Cerebral palsy
Immunocompromised[2] individuals of any age	**Higher risk**: Therapeutics should always be recommended for immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying immune status, regardless of age or vaccine status [1,2]			Intellectual disability Sickle cell disease Moderate or severe kidney disease (eGFR <60 mL/min) Moderate or severe liver disease (e.g. Child Pugh, Class B or C cirrhosis)
Pregnancy	**Higher risk**[3]	Standard risk	Standard risk	

1. Evidence for the safety and efficacy of sotrovimab and nirmatrelvir/ritonavir (Paxlovid) in children <18 years of age is limited. While early evidence on risk factors for moderate and severe COVID-19 in children is emerging, the ability to reliably predict disease progression in children remains very limited, and the frequency of progression is rare. While not routinely recommended in children <18 years of age, the use of these agents may be considered in exceptional circumstances (e.g. severe immunocompromise and/or multiple risk factors, clinical progression) on a case-by-case basis. Multidisciplinary consultation with Infectious Diseases (or Pediatric Infectious Diseases) and the team primarily responsible for the child's care is recommended to review the individual consideration of these medications.
2. Examples of immunocompromised or immunosuppressed individuals include receipt of treatment for solid tumours and hematologic malignancies (including individuals with lymphoid malignancies who are being monitored without active treatment), receipt of solid-organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency (e.g. DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good's syndrome, hyper IgE syndrome), advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e. ≥20 mg prednisone or equivalent per day when administered for ≥2 wk), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumour-necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.
3. Therapeutics should always be recommended for pregnant individuals who have received zero vaccine doses.

Prevention (accurate as of July 2023)

- complete series of mRNA COVID-19 vaccine (Moderna (Spikevax®) or Pfizer-BioNTech (Comirnaty®)) for all ages ≥6 mo who do not have contraindications, with boosters as per public health guidance

Skin and Soft Tissue Infections

Cellulitis

Definition

- acute infection of the skin principally involving the dermis and subcutaneous tissue

Etiology

- common causative agents: β-hemolytic streptococci (most common cause of non-purulent cellulitis), *S. aureus*, and occasionally *S. lugdunensis*
- immunocompromised patients or water exposure: may also include GN rods and fungi
- bite wounds: consider skin flora of "bitee" and mouth flora of "biter"
- risk factors
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema, DM, and cracked skin in feet/toes (tinea pedis)

Clinical Features

- pain, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
- can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

Investigations
- CBC and differential; blood C&S if patient has malignancy, severe systemic features, or unusual predisposing factors, such as immersion injury, animal bites, neutropenia, and severe cell-mediated immunodeficiency
- skin swab ONLY if open wound with pus

Treatment
- consult local guidelines for appropriate antibiotic therapy
- antibiotics: cephalexin (broader coverage if risk factors for GN rods)
- if extensive erythema or systemic symptoms, consider cefazolin IV
- if MRSA is suspected, empiric coverage for MRSA may be considered (see *A Simplified Look at Antibiotics, ID46*)
- limb rest and elevation may help reduce swelling

Necrotizing Fasciitis

Definition
- life- and limb-threatening infection of the deep fascia characterized by rapid spread

Etiology
- two main forms
  - Type I: polymicrobial infection – aerobes and anaerobes (e.g. *S. aureus, Bacteroides, Enterobacterales*)
  - Type II: monomicrobial infection with GAS, or less commonly *S. aureus*

Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema
- edema ± crepitus (subcutaneous gas from anaerobes)
- infection spreads rapidly
- rapid onset of systemic symptoms (e.g. tachycardia, hypotension, lightheadedness, disorientation, lethargy, and fever)
- late findings
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of hemorrhagic bullae
  - loss of sensation in the affected area (paresthesias)

Investigations
- clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
- blood and tissue C&S
- serum creatine kinase (CK) – elevated CK usually means myonecrosis (a late sign)
- plain film x-ray or CT (soft tissue gas may be visualized)
- surgical exploration for debridement of infected tissue

Treatment
- resuscitation with IV fluids
- emergency surgical debridement to confirm diagnosis and remove necrotic tissue (may require amputation)
- IV antibiotics
  - unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin if MRSA is considered
  - Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  - Type II (monomicrobial): with confirmed GAS infection, penicillin G + clindamycin IV; with confirmed S. aureus infection, cefazolin (or cloxacillin) + clindamycin IV
  - with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIG

Acquired Oral Lesions

Etiology
- infection (e.g. candidiasis, gonococcal infection, and HSV)
- malignancy (e.g. adenocarcinoma, leukoplakia)
- poor oral hygiene (e.g. caries, periodontal disease)
- trauma (e.g. abuse)
- toxic ingestion
- xerostomia (e.g. age, medications)
- systemic diseases (e.g. lichen planus, Behçet disease)

Table 15. Comparison between Oral Infection vs. Oral Carcinoma

	Oral Candidiasis	Oral Squamous Cell Carcinoma
Risk Factors	Antibiotics, chemotherapy, and radiation therapy Immunocompromised, inhaled corticosteroids Age – infants, older adults with dentures	Tobacco use (smoked and smokeless) Betel use Alcohol HPV, especially HPV-16
Morphology	Pseudomembranous: confluent, white patches or plaques, can be wiped off with a gauze, exposing an erythematous base Atrophic candidiasis: red patches localized mainly to the palate and dorsum of the tongue	A lesion of three or more weeks duration: Red or red and white lesion Ulcer Lump Especially when in combination or if indurated (firm on palpation)
Diagnosis	Cytology, biopsy, or culture	Biopsy and histopathologic examination
Treatment	Topical antifungal	Referral to ENT

Gastrointestinal Infections

- see Gastroenterology, G31 and Pediatrics, P44

Traveller's Diarrhea

- see Gastroenterology, G18

Chronic Diarrhea

- see Gastroenterology, G19

Peptic Ulcer Disease *(Helicobacter pylori)*

- see Gastroenterology, G13

Bone and Joint Infections

Septic Arthritis

Definition
- infection of one or more joints by pathogenic microbes

Routes of Infection
- hematogenous (most common)
  - from distant infection (e.g. abscesses, wound infection, and bacteremia)
- direct inoculation via skin/trauma
  - iatrogenic (e.g. surgery, arthroscopy, arthrocentesis, joint injection)
  - trauma (e.g. open wounds around the joint, penetrating trauma)
- contiguous spread (e.g. septic bursitis, osteomyelitis)

Etiology
- gonococcal
  - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* spp. (Group A and B)
  - GNs: affect neonates, elderly, injection drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae*: affects children <4 yr
  - *Haemophilus influenzae* type B (Hib) now rare due to Hib vaccine: consider in unvaccinated children
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* spp.: prosthetic joints
- if culture-negative: partially treated infection (prior to oral antibiotics), reactive arthritis, rheumatic fever, less common bacterial causes such as *Borrelia* spp. (Lyme disease) or *Tropheryma whipplei* (Whipple's disease), and non-infectious causes

Medical Emergency
Septic arthritis is a medical emergency! If untreated, rapid joint destruction will occur

Disseminated Gonococcal Infection Triad
Migratory arthralgias
Tenosynovitis next to inflamed joint
Pustular skin lesions

Risk Factors
- gonococcal
- age <40 yr, multiple partners, unprotected intercourse, MSM
- non-gonococcal
  - most affected children are previously healthy with no risk factors: occasionally preceding history of minor trauma
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (e.g. rheumatoid arthritis, osteoarthritis)
  - immunocompromised (e.g. DM, chronic kidney disease, alcohol use disorder, cirrhosis)
  - loss of skin integrity (e.g. cutaneous ulcer, skin infection)
  - age >80 yr

Intra-articular steroids are contraindicated until septic arthritis has been excluded

Clinical Features of Gonococcal Arthritis
- two forms (although often overlap):
  - septic arthritis form: local symptoms in involved joint (swelling, warmth, pain, inability to weight bear, decreased range of motion)
  - bacteremic form: systemic symptoms of fever, malaise, chills

Clinical Features of Non-Gonococcal Arthritis
- acute onset of pain, swelling, warmth, decreased range of motion ± fever and chills; in children, refusal to weight bear
- most often in large weight-bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)

Investigations
- consider rheumatologic causes for monoarthritis (see Rheumatology, Table 4, RH5)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal, and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory, CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBCs (>15000/mm ^{3}; likelihood of infection increases with increasing WBCs), PMNs >90%, culture positive
  - growth of *N. gonorrhoeae* from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment

IWGDF Guidance on the Diagnosis and Management of Foot Infections in Persons with Diabetes - Recommendations for Diagnosing Osteomyelitis
Diabetes Metab Res Rev 2016;32:45-74
Perform a probe-to-bone test for an infected open wound; a negative test likely rules out osteomyelitis in low-risk patients, while a positive test is likely diagnostic in high-risk patients.
In suspected cases, dramatically elevated serum inflammatory markers (especially ESR) are suggestive of osteomyelitis.
When in doubt, positive results on microbiological or histological exam of an aseptic bone sample are usually required for a definitive diagnosis of bone infection.
Bone infection is probable if there are positive results on a combination of diagnostic tests (probe-to-bone, serum inflammatory markers, plain x-ray, MRI, or radionuclide scanning).
For all cases of non-superficial diabetic foot infection, plain x-rays of the foot should be obtained.
When advanced imaging is required for diagnosis, MRI is preferred.

Treatment
- medical
  - empiric IV antibiotics: specific choice depends on clinical scenario and local guidelines; for most adults, cefazolin ± vancomycin is reasonable; for fully vaccinated children, cefazolin or cloxacillin IV unless MRSA is a consideration – delay may result in joint destruction
  - Gram stain and cultures guide subsequent treatment
  - gonococcal: ceftriaxone (+ azithromycin for concurrent treatment of *C. trachomatis*), 7 d of therapy usually sufficient
  - non-gonococcal: antibiotics against *Streptococcus* spp. (2-3 wk IV followed by PO), *S. aureus* (4 wk IV minimum), or GNB (4 wk, newer evidence suggests early switch to PO is safe and effective)
- surgical intervention if (see Orthopedic Surgery, OR11)
  - would consider surgical intervention on all cases of septic arthritis if possible
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement, especially in paediatric population
  - prosthetic joint
- daily joint aspirations until culture sterile
- physiotherapy

See Landmark Infectious Disease Trials table for more information on the OVIVA trial. It details whether oral antibiotic therapy is noninferior to IV antibiotic therapy for the management of complex orthopaedic infections.

Prognosis
- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: in children, generally good outcome if treated promptly; in adults, up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections

Etiology
- neuropathy, peripheral vascular disease, and hyperglycemia contribute to foot ulcers that heal poorly, and are predisposed to infection
- organisms in mild infection: *Streptococcus* spp., *S. aureus*
- organisms in moderate/severe infection: polymicrobial with aerobes (*S. aureus, Streptococcus, Enterococcus*, GNB) and anaerobes (*Peptostreptococcus, Bacteroides, Clostridium*)

Clinical Features
- not all ulcers are infected
- consider infection if: probe to bone (see below), ulcer present >30 d, recurrent ulcers, trauma, PVD, prior amputation, loss of protective sensation, renal disease, or history of walking barefoot

- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) OR the presence of pus
- ± crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone: osteomyelitis
- infection severity
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint) or erythema >2 cm
  - severe = infection in a patient with systemic toxicity (fever, tachypnea, leukocytosis, tachycardia, hypotension)

Investigations
- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infections)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages) or MRI/bone scan if high clinical suspicion
- if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity

Treatment
- mild to moderate: cefazolin or cephalexin
- severe: options include: 1. ceftriaxone + metronidazole; 2. piperacillin/tazobactam ± vancomycin; 3. meropenem ± vancomycin
- optimize glycemic control, pressure offloading, wound care, consider revascularization
  - this is empiric treatment, and specific treatment needs to be adjusted based on culture and response to therapy

Osteomyelitis

- see Orthopedic Surgery, OR11

Cardiac Infections

Infective Endocarditis

Definition
- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
- leaflet vegetations are made of platelet-fibrin thrombi, WBCs, and bacteria

Risk Factors and Etiology
- predisposing conditions
  - high-risk: prosthetic cardiac valve, previous infective endocarditis (IE), congenital heart disease (unrepaired, repaired within 6 mo, or repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - moderate risk: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - low/no risk: secundum atrial septal defect (ASD) or surgically repaired ASD, ventricular septal defect (VSD), patent ductus arteriosus (PDA), mitral valve (MV) prolapse, ischemic heart disease, previous coronary artery bypass graft (CABG)
  - opportunistic bacteremia: IVDU, indwelling venous catheter, hemodialysis, poor dentition, DM, HIV
- frequency of valve involvement MV>>aortic valve (AV)>tricuspid valve (TV)>pulmonary valve (PV)
  - in 50% of IVDU-related IE the tricuspid valve is involved

Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors

Native Valve	IVDU	Prosthetic Valve (recent surgery <2 mo)	Prosthetic Valve (remote surgery >2 mo)
***Streptococcus*[1] (36%)**	***S. aureus* (68%)**	***S. aureus* (36%)**	***Streptococcus* (20%)**
***S. aureus* (28%)**	***Streptococcus* (13%)**	***S. epidermidis* (17%)**	***S. aureus* (20%)**
***Enterococcus* (11%)**	*Enterococcus*	*Enterococcus*	***S. epidermidis* (20%)**
S. epidermidis	GNB	GNB	***Enterococcus* (13%)**
GNB	*Candida*	Other[2]	Other[2]
Other[2]	Other[3]		

Organisms in bold are the most common isolates
1. *Streptococcus* includes mainly viridans group streptococci
2. Other includes less common organisms such as:
   - *Streptococcus gallolyticus* (previously known as *S. bovis*; usually associated with underlying GI malignancy and cirrhosis)
   - Culture-negative organisms including *Abiotrophia, Granulicatella, Bartonella, Coxiella, Chlamydia, Legionella, Brucella*
   - *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella*, and *Kingella* (HACEK)
   - *Candida*
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = *Pseudomonas*, saliva = oral flora, toilet water = GI flora)

Clinical Features
- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia

- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute mitral regurgitation (MR), atrial regurgitation (AR))
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), headache (mycotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
  - Osler's nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth's spots (retinal hemorrhage with pale centre)

Clinical Features of Infective Endocarditis

FROM JANE
Fever
Roth's spots
Osler's nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhages (i.e. splinter hemorrhages)
Emboli

Diagnosis

- Modified Duke Criteria
  - definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  - possible diagnosis if: 1 major + 1 minor, OR 3 minor

Table 17. Modified Duke Criteria

Major Criteria (2)
1. Positive blood cultures for IE • Typical microorganisms for IE from 2 separate blood cultures (*Streptococcus viridans*, HACEK group, *Streptococcus gallolyticus, Staphylococcus aureus*, community-acquired enterococci) OR • Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart OR • All of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1 h apart OR • Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800 2. Evidence of endocardial involvement • Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve); and new valvular regurgitation (insufficient if increase or change in pre-existing murmur)
Minor Criteria (5)
1. Predisposing condition (abnormal heart valve, IVDU) 2. Fever (38.0°C/100.4°F) 3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracerebral hemorrhage (ICH), conjunctival hemorrhages, Janeway lesions 4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler's nodes, Roth's spots 5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE

TEE Transesophageal echo
TTE Transthoracic echo

Investigations

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of an endovascular infection (e.g. IE)
- repeat blood cultures (at least 2 sets) after 48-72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), erythrocyte sedimentation rate (ESR) (increased), rheumatoid factor (RF) (+), urea/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- echo findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) indicated for all suspected IE, inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

Treatment

- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment unless patient is septic
  - empiric antibiotic therapy if patient is unstable; administer ONLY after blood cultures have been taken. Generally, *S. aureus*, coagulase-negative *Staphylococcus* (CNST), and GN coverage is important
    - first line empiric treatment for native valve: vancomycin + ceftriaxone OR gentamicin
    - first line empiric treatment for prosthetic valve: vancomycin + gentamicin + rifampin
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism, and susceptibilities
  - monitor for complications of IE (e.g. heart failure (HF), conduction block, new emboli) and complications of antibiotics (e.g. renal disease)
  - post-treatment prophylaxis only recommended for high-risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure, or musculoskeletal tissue

- dental/respiratory procedures: amoxicillin single dose 30-60 min prior; clindamycin if truly penicillin-allergic
- infected skin/soft tissue procedures: cephalexin single dose 30-60 min prior; clindamycin if truly penicillin-allergic (modify based on etiology of skin/soft tissue infection)

- surgical
  - most common indication is refractory CHF
  - other indications include: valve ring abscess, valve perforation, unstable prosthesis, large vegetation >1 cm, recurrent emboli despite adequate antimicrobial treatment, antimicrobial failure (persistently positive blood cultures), fungal etiology, *S. aureus* on a prosthetic valve

Prognosis

- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess, embolization, persistent bacteremia, altered mental status
- mortality: prosthetic valve IE (25-50%), non-IVDU *S. aureus* IE (30-45%), IVDU *S. aureus* or streptococcal IE (10-15%)

CNS Infections

Meningitis

- see Pediatrics, P65

Definition

- inflammation of the meninges

Etiology

Table 18. Common Organisms in Meningitis

Bacterial			Viral	Fungal	Other
Age 0-4 wk	**Age 1-3 mo**	**Age >3 mo**			
GBS *E. coli* *L. monocytogenes* *Klebsiella*	GBS *E. coli* *S. pneumoniae* *N. meningitidis* *H. influenzae*	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* (likely if age >50 and comorbidities)	HSV-1, 2 VZV Enteroviruses Parechoviruses West Nile	Cryptococcus Coccidioides	Lyme disease Neurosyphilis TB

Risk Factors

- lack of immunization against *H. influenzae* type B, *S. pneumoniae*, and *N. meningitidis* in children
- most cases of bacterial meningitis are due to hematogenous spread from a mucosal surface (nasopharynx)
- direct extension from a parameningeal focus (otitis media, sinusitis) less common
- penetrating head trauma or iatrogenic
- anatomical meningeal defects – CSF leaks
- immunodeficiency (e.g. corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency, etc.)
- contact with colonized or infected persons

Clinical Features

- neonates and children: fever, lethargy, irritability, vomiting, poor feeding
- older children and adults: fever, headache, neck stiffness, confusion, lethargy, altered LOC, seizures, focal neurological signs, nausea/vomiting, photophobia, papilledema
- petechial rash in meningococcal meningitis (purpura fulminans), seen more frequently on trunk or lower extremities

Investigations

- blood work: CBC and differential, electrolytes (for SIADH), blood C&S
  - CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
  - AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
  - PCR for HSV, VZV, enteroviruses; in infants <6 mo, parechoviruses
  - West Nile virus serology in blood and CSF during summer and early fall if viral cause suspected
- imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

Table 19. Typical CSF Profiles for Meningitis

CSF Analysis	Bacterial	Viral
Glucose (mmol/L)	Decreased	Normal
Protein (g/L)	Markedly increased	Increased
WBC	500-10000/μL	10-500/μL
Predominant WBC	Neutrophils	Lymphocytes

See Landmark Infectious Diseases Trials for more information on the POET trial, which investigated the efficacy and safety of shifting from IV to oral antibiotics in patients with IE.

Corticosteroids for Acute Bacterial Meningitis
Cochrane DB Syst Rev 2015;CD004405
Purpose: To examine the effect of adjuvant corticosteroid therapy vs. placebo on mortality, hearing loss, and neurological sequelae with acute bacterial meningitis.
Methods: RCTs of corticosteroids for acute bacterial meningitis.
Results: 25 studies, 4121 participants. Corticosteroids were associated with non-significant mortality reductions (RR 0.90, 95% CI 0.80-1.01). Corticosteroids were associated with lower rates of hearing loss (RR 0.74, 95% CI 0.63-0.87) and neurological sequelae (RR 0.83, 95% CI 0.69-1.00). Corticosteroids were associated with increase in recurrent fever (RR 1.27, 95% CI 1.09-1.47).
Conclusions: Corticosteroids significantly reduced hearing loss and neurological sequelae but did not reduce mortality. Data supports use in high-income countries but no benefit in low-income countries.

Brudzinski's Sign
Passive neck flexion causes involuntary flexion of hips and knees

Kernig's Sign
Resistance to knee extension when hip is flexed to 90°

Jolt Accentuation of Headache
Headache worsens when head turned horizontally at 2-3 rotations; more sensitive than Brudzinski's and Kernig's

CSF Gram Stain Findings
- *S. pneumoniae* – GP diplococci
- *N. meningitidis* – GN diplococci
- *H. influenzae* – Pleomorphic GN coccobacilli
- *L. monocytogenes* – GP rods

Does this Adult Patient have Acute Meningitis?
JAMA 1999;281:175-181
Study: Systematic review of literature analyzing the accuracy and precision of the clinical examination in the diagnosis of adult meningitis.
Results: Clinical history items have a low accuracy for the diagnosis of meningitis in adults. The sensitivity for headaches is 50% and the sensitivity for nausea/vomiting is 30%. On physical examination, absence of fever, neck stiffness, and altered mental status eliminates meningitis with a sensitivity of 99%.
Conclusions: The clinical examination aids in excluding a diagnosis of meningitis in adults with a low-risk clinical presentation. In high-risk patients, clinicians need to proceed directly to lumbar puncture given the serious implications of the infection.

Treatment
- bacterial meningitis is a medical emergency: do not delay antibiotics for CT or LP
- empiric antibiotic therapy
  - age ≤28 d: ampicillin + cefotaxime
  - age 29 d-3 mo: ceftriaxone/cefotaxime + vancomycin ± ampicillin
  - age >3 mo: ceftriaxone + vancomycin
    - add ampicillin IV if risk factors for infection with L. monocytogenes present: age >50, alcohol use disorder, immunocompromised
- steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics
  - continue in those patients with proven pneumococcal meningitis
  - not recommended for patients with suspected bacterial meningitis in some resource-limited countries
  - not recommended for neonatal meningitis

Prevention
- see Pediatrics, P65
- immunization
  - children: immunization against *H. influenzae* type B (Pentacel®), *S. pneumoniae* (Synflorix®, Prevnar-13®), *N. meningitidis* (Menjugate®, Menactra®, Nimenrix®, Menveo®, Bexsero®)
  - adults: immunization against *N. meningitidis* in selected circumstances (immunocompromised, outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with H. influenzae type B should be treated with rifampin if they live with an inadequately immunized (<4 yr) or immunocompromised child (<18 yr); ciprofloxacin, rifampin, or ceftriaxone if close or household contact of a patient with *N. meningitidis*; meningococcal vaccines are also recommended for post-exposure prophylaxis for close contacts and in outbreak control

Prognosis
- complications
  - death, headache, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

Encephalitis

Definition
- inflammation of the brain parenchyma

Etiology
- identified in only 40-70% of cases
  - when cause is identified, the most common etiology is viral: HSV, VZV, EBV, CMV, enteroviruses, parechoviruses, West Nile and other arboviruses, influenza and other respiratory viruses, HIV, mumps, measles, rabies, polio
  - bacteria: *L. monocytogenes*, mycobacteria, spirochetes (Lyme, syphilis), *Mycoplasma pneumoniae*
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. acute disseminated encephalomyelitis (ADEM))

Pathophysiology
- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response viruses may reach the CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial, temporal, and inferior frontal lobes
  - associated with HSV-1, less likely caused by HSV-2
- influenza and other respiratory viruses are associated with acute necrotizing encephalopathy (ANE); likely mediated by pathogen-initiated immune response

Clinical Features
- constitutional: fever, chills, malaise, nausea/vomiting
- meningeal involvement (meningoencephalitis): headache, nuchal rigidity
- parenchymal involvement: seizures, altered mental status, focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioural disturbance
  - usually rapidly progressive over several days and may result in coma or death
  - common sequelae: memory and behavioural disturbances
  - rare complication: development of encephalopathy and Kluver-Bucy syndrome characteristics 1 mo after completion of treatment for HSV encephalopathy

Public Health Agency of Canada Indications for Adult Immunization

Pneumococcal Polysaccharide Vaccine (i.e. Pneumovax®)
≥65 yr (option to also give pneumococcal conjugate vaccine; if so, to give polysaccharide vaccine 8 wk after conjugate vaccine)

Pneumococcal Polysaccharide Vaccine (i.e. Pneumovax®) and Pneumococcal Conjugate Vaccine
Chronic cardiovascular/respiratory/hepatic/renal disorders, asplenia, sickle cell, or immunosuppression (polysaccharide vaccine to be given 8 wk after pneumococcal conjugate vaccine)

Meningococcal Quadrivalent Vaccine (Menactra® or Menomune®)
Healthy young adults
Asplenia
Travellers to high-risk areas
Military recruits or laboratory personnel
Complement, factor D, or properdin deficiency or acquired terminal complement deficiency through receipt of eculizumab

Multicomponent Meningococcal Serogroup B Vaccine (Bexsero®)
Asplenia
Military recruits or laboratory personnel
Complement, factor D, or properdin deficiency, or acquired terminal complement deficiency through receipt of eculizumab

Meningitis and encephalitis patients can be distinguished based on their cerebral function. Cerebral function is abnormal in encephalitis patients (e.g. altered mental status, motor or sensory deficits, altered behaviour, speech or movement disorders), but may be normal in patients with meningitis. Note however, that there is considerable overlap between the two syndromes ("meningoencephalitis")

Investigations
- CSF: opening pressure, cell count and differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses/parechoviruses, *M. pneumoniae*, and selectively for other less common etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. EBV, West Nile virus, rabies, *Bartonella henselae*)
- imaging/neurologic studies: CT, MRI, EEG to define affected anatomical sites
- invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges

Treatment
- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out

Generalized Tetanus

Etiology and Pathophysiology
- caused by *Clostridium tetani*: motile, spore forming, anaerobic GP bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wounds, burns, non-sterile surgeries, or deliveries)
- upon inoculation, spores develop into *C. tetani* bacilli that produce tetanus toxins
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

Clinical Features
- generalized tetanus
  - initially present with painful spasms of masseters (trismus or "lockjaw")
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
- autonomic hyperactivity
  - diaphoresis, tachycardia, HTN, fever as illness progresses

Antimicrobial therapy (e.g. metronidazole) may fail to treat C. tetani unless adequate wound debridement is performed

Investigations
- primarily a clinical diagnosis, often although not always with a history of a traumatic wound and lack of immunization
- culture wounds, CK may be elevated

Treatment
- stop toxin production
  - wound debridement to clear necrotic tissue and spores
  - antimicrobial therapy: IV metronidazole (effective alternative: IV penicillin G)
- neutralize unbound toxin with tetanus immune globulin (TIg)
- supportive therapy: intubation, spasmolytic medications (benzodiazepines), quiet environment, cooling blanket

control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate

Prevention
- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see Pediatrics, P65 and Emergency Medicine, ER17)

Rabies

Definition
- acute progressive encephalitis caused by RNA virus (genus Lyssavirus of the Rhabdoviridae family)

Etiology and Pathophysiology
- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoons, skunks, bats, foxes, cats, and dogs; monkeys also a risk in the tropics and sub-tropics
- transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
  - almost all cases due to bites
  - animals can be carriers for several days before manifest signs of disease

- virus travels via retrograde axonal transport from PNS to CNS
- virus multiplies rapidly in brain, then spreads to other organs, including salivary glands
- development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
  - infected animal can transmit rabies virus as soon as it shows signs of disease

Clinical Features
- five stages of disease
  1. incubation period
     - 1-3 mo on average (can range from days to years, depending on distance from bite site to CNS)
  2. prodrome (<1 wk)
     - low-grade fever, malaise, anorexia, nausea/vomiting, headache, sore throat
     - pain, pruritus, and paresthesia may occur at wound site
     - once prodromal symptoms develop, there is rapid, irreversible progression to death
       - progression from prodrome to coma and death may occur without an intervening acute neurologic syndrome
  3. acute neurologic syndrome: 2 types (<1 wk)
     a. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia, hypersalivation, fever, seizures
       - painful pharyngeal spasms on encountering gust of air or swallowing water cause aerophobia and hydrophobia, respectively

     b. paralytic: quadriplegia, loss of anal sphincter tone, fever
  4. coma
     - complete flaccid paralysis, respiratory, and cardiovascular failure
  5. death (within days to weeks of initial symptoms)

Investigations
- purpose of diagnosis by investigations is to limit patient contact with others and to identify others exposed to the infectious source
- antemortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, serum, CSF
- post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in neurons)

Treatment
- post-exposure prophylaxis depends on regional prevalence and circumstances surrounding injury
- mandatory to report animal bite/contact that may result in rabies to Public Health Authority
- if not previously immunized:
  - wound care: clean wound promptly and thoroughly with soap and running water for 15 min
  - passive immunization: rabies immunoglobulin (RIG) infiltrated into wound site, with any remaining volume administered IM in anatomical site distant from vaccine administration
    - due to variable response rates, vaccine should not be administered into gluteal muscle
  - active immunization: inactivated human diploid cell rabies virus vaccine (HDCV) – series of 4 shots post-exposure on d 0, 3, 7, and 14
    - vaccine administered into deltoid
- if previously immunized:
  - wound care: clean wound promptly and thoroughly with soap and running water for 15 min
  - two doses of HDCV into deltoid on d 0 and 3
  - no RIG administered
- treatment is supportive once victim manifests signs and symptoms of disease

Prevention
- pre-exposure vaccination
  - recommended for high-risk persons: laboratory staff working with rabies, veterinarians, animal and wildlife control workers, long-term travellers to endemic areas

Systemic Infections

Sepsis and Septic Shock

- see Respirology, R32

Definitions
- bacteremia: bacteria in blood from primary bloodstream infection or secondary to infection of another body system
- sepsis: severe organ dysfunction resulting from dysregulated host response to infection
  - organ dysfunction identified via acute change in SOFA score ≥2 points
  - qSOFA score used initially to screen patients for suspected sepsis using three criteria:
    1. respiratory rate ≥22/min
    2. sBP ≤100 mmHg
    3. altered mentation (GCS <15)
- septic shock: subset of sepsis with circulatory and cellular/metabolic dysfunction; clinically defined in cases where despite adequate volume resuscitation there is both
    1. persistent hypotension requiring vasopressors to maintain MAP ≥65 mmHg AND
    2. serum lactate >2 mmol/L

SOFA score >2 = 10% mortality risk in patient with suspected infection
Hospital mortality with septic shock >40%

qSOFA score
1. Respiratory rate ≥22/min
2. sBP ≤100 mmHg
3. Altered mentation (GCS <15)

Pathophysiology
- causative agents are identified in only 50-70% of cases
- when organisms are identified, GP and GN organisms are the cause in 90% of cases
- bacteremia → local immune response → pro-inflammatory cytokine release → spread of immune response beyond local environment → unregulated, exaggerated systemic immune response → vasodilation and hypotension → distributive shock and reduced O_2 delivery to tissues → anaerobic metabolism and lactic acid production → metabolic acidosis → multiple organ failure

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016 re-defined sepsis using the Sequential Organ Failure Assessment (SOFA) score for diagnosis and Quick-SOFA (qSOFA) for screening of end-organ failure. The terms severe sepsis and systemic response inflammatory response syndrome (SIRS) are no longer part of the sepsis definition

Clinical Features
- history: symptoms and signs specific to an infectious source (e.g. cough, headache, dysuria, purulent exudate, rash)
- general symptoms of infection: fever, chills, pain, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: abnormal vitals (e.g. fever, tachypnea, tachycardia, hypotension), flushed skin, altered mental status, local signs of infection (e.g. pharyngitis, septic arthritis, neck stiffness, skin wounds/ulcers, or murmurs)

Investigations
- CBC and differential, electrolytes, urea, creatinine, liver enzymes, ABG, lactate, INR, PTT, troponin, blood C&S x2, urinalysis, urine C&S, and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus of infection)
- nasopharyngeal swab/stool/sputum cultures, throat swabs, genital swab, LP as indicated

Treatment (see Respirology, R32)
- respiratory support: O_2 ± intubation
- cardiovascular support: IV fluids ± blood transfusion + vasopressors + ICU
- IV antibiotics (empirical, guided by suspected source)
  - consider broad spectrum antibiotics (e.g. piperacillin/tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology or focus of infection, and local microbial susceptibilities (± aminoglycoside for drug-resistant Gram-negatives or vancomycin for MRSA)
  - breadth of empiric coverage should take into account: i) estimated adequacy of spectrum of activity and ii) degree of instability or severity of infection
  - narrow once organism and susceptibilities are known
- source control: procedure to control focus of infection (catheter removal, abscess drainage)
- hydrocortisone IV may be added in patients with septic shock unresponsive to fluid resuscitation and vasopressors

Leprosy (Hansen's Disease)

Etiology
- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

Clinical Features
- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  - i. paucibacillary "tuberculoid" leprosy (intact cell-mediated immune response)
    - ≤5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
    - early nerve involvement, enlarged peripheral nerves, neuropathic pain
    - may be self-limited, stable, or progress over time to multibacillary "lepromatous" form
  - ii. multibacillary "lepromatous" leprosy (weak cell-mediated immune response)
    - ≥6 lesions, symmetrical distribution
    - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
    - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  - iii. borderline leprosy
    - lesions and progression lie between tuberculoid and lepromatous forms

Investigations
- skin biopsy down to fat or slit skin smears for AFB staining, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

Treatment
- regimens based on WHO recommendations
- paucibacillary: dapsone daily + rifampin monthly + clofazimine monthly AND low dose clofazimine once daily x 6 mo
- multibacillary: dapsone daily + rifampin monthly + clofazimine monthly x 12 mo AND low dose clofazimine once daily for 12 mo

- treatment of leprosy (along with other precipitants of immune responsiveness such as viral illness, immunization, hormonal fluctuations of pregnancy, and parturition) can cause an immune reaction to killed or dying bacteria (e.g. erythema nodosum leprosum [a type of antigen-antibody complex deposition panniculitis] and reversal reaction [upgrading cell-mediated immune response]):
  - symptomatic management with NSAIDs if mild
  - prednisone with 12-24 wk taper if severe
  - thalidomide for erythema nodosum leprosum

Prognosis
- curable with WHO approved treatment regimens
- complications: muscle atrophy, contractures, blindness, trauma/superinfection of lesions, crippling/loss of digits and limbs, erythema nodosum leprosum, social stigmatization due to clofazimine hyperpigmentation
- long post-treatment follow-up warranted to monitor for relapse and immune

Lyme Disease

Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (North America), *B. garinii, B. afzelii* (Europe and Asia)
- transmitted by *Ixodes* tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- as a result of climate change, Lyme disease has spread into higher latitudes. In Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick, and Nova Scotia, as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white-tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas, but may start earlier in the spring or later in the fall as a result of warmer winters due to climate change
- infection usually requires >36 h tick attachment
- as a result of climate change, other tick-borne diseases are expected to increase in prevalence: Anaplasmosis, Babesiosis, Powassan virus, and B. miyamotoi disease

BAKE a Key Lyme Pie
Bell's palsy
Arthritis
Kardiac block
Lyme
Erythema chronicum migrans

Clinical Features
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, headache, myalgias
  - erythema migrans: expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) at site of tick bite
- stage 2 (early disseminated stage: weeks post-infection)
  - CNS: aseptic meningitis, CN palsies (CN VII palsy), peripheral neuritis
  - cardiac: heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early-stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronicum atrophicans (due to B. afzelii)
  - neurologic: encephalopathy, meningitis, neuropathy

Investigations
- order Public-Health-Lab-approved Lyme disease testing and interpret results on basis of symptoms
- a negative test for Lyme disease does not preclude a tick-borne disease; further testing may be indicated if symptoms are present

Prevention
- early identification, investigation of symptoms, and reporting of tick-borne illnesses
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks, and prompt removal of tick
- doxycycline single dose prophylaxis within 72 h of removal of an engorged Ixodes scapularis tick in hyperendemic area (local rate of infection of ticks ≥20%) for patients >8 yr who are not pregnant or lactating

Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone or doxycycline

Toxic Shock Syndrome

Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF)
- course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- staphylococcal Toxic Shock Syndrome (TSS) involves the production of superantigen toxic shock syndrome toxin 1 (TSST-1)
- streptococcal TSS involves the production of superantigens SPEA, SPEB, SPE

Risk Factors
- staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or cesarean or surgical infections)
- streptococcal: minor trauma, surgical procedures, preceding viral illness (e.g. chickenpox), use of NSAIDs

Clinical Features and Investigations
- acute onset
- staphylococcal TSS
  - T >38.9°C
  - sBP ≤90 mmHg
  - diffuse erythroderma with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
- streptococcal TSS
  - sBP ≤90 mmHg
  - isolation of GAS from a normally sterile site (e.g. blood, pleural, tissue biopsy, or surgical wound)
  - ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment, erythematous macular rash that may desquamate

Treatment
- supportive care, fluid resuscitation, surgical debridement of infected tissue
- streptococcal: IV penicillin and clindamycin ± IVIG
- staphylococcal: for methicillin-susceptible *S. aureus*: clindamycin + cloxacillin (IV); for MRSA: clindamycin + vancomycin x 10-14 d

Cat Scratch Disease

Etiology
- *Bartonella henselae*: intracellular bacteria
- cat-to-human transmission via cat scratch/bite

Clinical Features
- skin lesion appears 30 d post-inoculation
- may be followed by fever, malaise, tender regional lymphadenopathy
- usually self-limited
- in some patients, organism may disseminate causing FUO, hepatosplenomegaly, retinitis, encephalopathy, infective endocarditis, uveitis
- in patients with advanced HIV, can present with violacious nodular skin lesions + underlying bone involvement, known as "bacilliary angiomatosis"

Investigations
- serology, PCR, lymph node biopsy

Treatment
- the disease may be self-limited but treatment is recommended by the Infectious Disease Society of America with a 5 d course of azithromycin for immunocompetent patients with mild to moderate illness
- needle aspiration of painful suppurative lymph nodes may hasten the relief of symptoms
- combination therapy consisting of doxycycline or azithromycin plus rifampin often used for disseminated disease (neuroretinitis, hepatosplenic involvement)

Rocky Mountain Spotted Fever

Etiology
- Rickettsia rickettsii: obligate intracellular GN organism
- reservoir hosts: rodents, dogs
- vectors: *Dermacentor* ticks in North America; *Rhipicephalus* ticks in Mexico and Central America
- organisms cause inflammation of endothelial lining of small blood vessels, leading to small hemorrhages and thrombi
- can cause widespread vasculitis leading to headache, and CNS changes; can progress to death if treatment is delayed

Clinical Features
- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, headache, myalgia, nausea/vomiting, anorexia
- macular rash appearing on d 2-4 of fever
  - begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  - occasionally "spotless" (10% of patients)

Investigations
- skin biopsy and serology (indirect fluorescent antibody test)

Treatment
- empiric doxycycline, usually 5-7 d (treat for 3 d after defervescence)

West Nile Virus

Epidemiology
- virus has been detected throughout the United States and much of southern Canada (Quebec, Ontario, Manitoba, Saskatechewan, Alberta)
- case-fatality rates in severe cases are ~10%

Transmission
- primarily from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation
- rising temperatures linked to increased mosquito survival and geographical range, increased biting rates, increased replication of virus within mosquitoes, shorter reproduction rates, and longer transmission seasons. Climate change also affects bird migration patterns and timing, causing changes in virus spread

Clinical Features
- 80% are asymptomatic
- most symptomatic cases are mild (West Nile fever): acute onset of headache, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis, and acute flaccid paralysis (especially in those >60 yr)

Investigations
- IgM antibody in serum or CSF is the best test (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- viral isolation by PCR from CSF, tissue, blood, and fluids (all have low sensitivity due to transient viremia)
- CSF: elevated lymphocytes and protein if CNS involvement

Treatment and Prevention
- treatment: supportive
- prevention: mosquito repellant (DEET, picaridin), drain stagnant water, community mosquito control programs

Syphilis

Etiology
- *Treponema pallidum*: thick motile spirochetes historically detectable by dark-field microscopy
- transmitted sexually, vertically, or parenterally (rare)

Clinical Features
- see Dermatology, D38 and Gynecology, GY30
- multi-stage disease
  1. primary syphilis (3-90 d post-infection)
     - painless chancre at inoculation site (any mucosal surface)
     - regional lymphadenopathy
     - acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment
  2. secondary syphilis = systemic infection (2-8 wk following chancre)
     - maculopapular non-pruritic rash including palms and soles
     - generalized lymphadenopathy, fever, malaise, headache, aseptic meningitis, ocular/otic syphilis
     - condylomata lata: painless, wart-like lesion on palate, vulva, or scrotum (highly infectious)
  3. latent syphilis
     - asymptomatic infection that follows untreated primary/secondary syphilis
     - early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
     - increased transmission risk with early latent; longer treatment duration required for late latent
  4. tertiary syphilis (1-30 yr post-infection)
     - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
     - aortic aneurysm and aortic insufficiency
  5. congenital syphilis
     - causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
     - most infected newborns are asymptomatic
     - clinical manifestations in early infancy include rhinitis (snuffles), lymphadenopathy, hepatosplenomegaly, pseudoparalysis (bone pain associated with osteitis), and rash (usually maculopapular and involving palms and soles)

Argyll Robertson Pupil
Accommodates but does not react to light

Those with Untreated 1° or 2° Syphilis
1/3 Cure
1/3 Latent indefinitely
1/3 3° syphilis

Causes of False Positive VDRL and RPR Tests

Viruses (mononucleosis, hepatitis)
Drugs and substance misuse
Rheumatic fever
Lupus and leprosy

- late onset manifestations (>2 yr of age) include saddle nose, saber shins, Clutton joints, Hutchinson's teeth, mulberry molars, rhagades, CN VIII deafness, interstitial keratitis, juvenile paresis

6. neurosyphilis
   - headache, dementia, difficulty in coordination, paralysis, sensory deficits, personality changes, Argyll-Robertson pupils, tabes dorsalis
   - can occur from secondary stage onward

Patients with 2° or 3° syphilis treated with penicillin may experience a Jarisch-Herxheimer reaction. Lysis of organisms releases pyrogens thought to cause fever, chills, myalgia, and flu-like symptoms that may last up to 24 h

Investigations

- syphilis tests are conducted by Public Health labs. Thus, order set for syphilis is simplified and does not require specification of which test to complete. Below are details on what tests are conducted at the Public Health lab
- initial screening tests: traditionally non-treponemal tests (RPR, VRDL), or treponemal tests in some jurisdictions (EIA, CMIA, CLIA)
- confirmatory tests: treponemal tests (TPPA, FTA-ABS, MHA-TP, TPI)
- LP for neurosyphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms, or with HIV and late latent/unknown duration syphilis; consider in others
- for congenital syphilis, LP is essential; long bone x-rays may also be helpful

VDRL Venereal Disease Research Laboratory
RPR Rapid Plasma Reagin
EIA Enzyme Immunoassay
CLIA ChemiLuminescent ImmunoAssay
CMIA ChemiLuminescent Microparticle ImmunoAssay
FTA-ABS Fluorescent Treponema Antibody-Absorption
MHA-TP Microhemagglutination Assay *T. pallidum*
TPPA *T. pallidum* Particle Agglutination Assay
TPI *T. pallidum* immobilization test

Treatment

- for 1°, 2°, early latent: benzathine penicillin G 2.4 million units IM x 1
- for 3°, late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- if truly allergic to penicillin: doxycycline 100 mg PO BID x 14 d is a second line therapy (x 28 d in late disease)
- for pregnant patients allergic to penicillin, oral desensitization techniques are considered safe
- neurosyphilis: aqueous penicillin G 16-24 million units/d IV x 14 d ± single dose of benzathine penicillin
- for congenital syphilis, penicillin G IV x 10 d
- see Family Medicine, FM47 for generalized STI workup

Tuberculosis

Etiology, Epidemiology, and Natural History

- 1/3 of the world's population is infected with TB
- contracted by aerosolized inhalation of *Mycobacterium tuberculosis*, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive, and replicate in macrophages
- inhalation and deposition in the lung can lead to one of the following outcomes:
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 90% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 1-2 yr of initial infection) at a pulmonary or extra-pulmonary site

Tuberculous Polyserositis
Pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)

Risk Factors

- social and environmental factors
  - birth in or extended travel to a country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  - the incidence of TB is 25 times higher in Canadian-born Indigenous peoples (highest in Inuit) compared to Canadian-born non-Indigenous peoples
  - personal/occupational contact, crowded living conditions, low socioeconomic status (SES), people experiencing homelessness, IDU
- host factors
  - immunocompromised (especially HIV), including extremes of age
  - immunosuppressed (TNF-α inhibitors, glucocorticoids)
  - silicosis
  - chronic kidney disease requiring dialysis
  - diabetes
  - malignancy and chemotherapy
  - substance use (e.g. drug use, alcohol use disorder, smoking)

Clinical Features

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms
  1. pulmonary TB
     - chronic productive cough + hemoptysis, fever, night sweats, weight loss, chest pain, anorexia
     - CXR consolidation or cavitation, lymphadenopathy, predominantly upper lung findings but variable
     - non-resolving pneumonia despite standard antimicrobial therapy
  2. miliary TB
     - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
     - CXR: multiple small 1-5 mm millet seed-like lesions throughout lung

3. extra-pulmonary TB
    - can occur in any organ - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott disease), adrenal (causing Addison disease), renal, ovarian

Investigations

- screening for latent TB may be done via TST or IFN-γ release assay (IGRA)
    - both can be used to diagnose prior TB infection. IGRA has fewer false positives as it does not detect antigens in BCG vaccine or most types of non-tuberculosis mycobacteria
        - neither should be used in adults for active TB diagnosis or monitoring anti-TB treatment response
        - TST preferred when repeat testing planned to assess risk of new infection (e.g. serial testing in healthcare)
- IGRA preferred when BCG vaccine after 1 y/o, vaccination more than once, or unable to return for reading
- diagnostic tests/investigations for active pulmonary TB
    - sputum specimens (either spontaneous or induced) should be collected for AFB smear and culture; the three specimens can be collected on the same day, a minimum of 1 h apart
    - BAL if other lung pathology (e.g. lung cancer) also suspected, or TB suspected despite negative sputum samples
    - CXR
        - classic triad: apical-posterior infiltrates, lung volume loss, cavitation
        - atypical features: hilar/mediastinal lymphadenopathy, non-cavitary infiltrates
        - signs of complications: endobronchial spread, pleural effusion, pneumothorax
        - Ghon complex: a parenchymal granuloma, indicating a previous tuberculosis infection, and a calcified hilar lymph node on the same side

Positive TST Test
If induration at 48-72 h
>5 mm if immunocompromised, close contact with active TB
>10 mm all others; positive PPD; CXR; decision to treat depends on individual risk factors
False(–): poor technique, anergy, immunosuppression, infection <10 wk or remotely
False(+): BCG after 12 mo of age in a low-risk individual, nontuberculous mycobacterial **(NTM)**
Booster effect: initially false(–) result boost to a true(+) result by the testing procedure itself (usually if patient was infected long ago so had diminished delayed type hypersensitivity reaction or if history of BCG)

Prevention

- primary prevention
    - airborne isolation for active pulmonary disease
    - BCG vaccine
        - ~80% effective against paediatric miliary and meningeal TB
        - effectiveness in adults debated (anywhere from 0-80%)
        - recommended in high-incidence communities in Canada for infants in whom there is no evidence of HIV infection of immunodeficiency; widely used in other countries
- prevention of reactivation of latent infection
    - rifampin (RIF) (10 mg/kg (600 mg maximum)) daily for 4 mo (active disease must be ruled out)
    - isoniazid (INH) (15 mg/kg (900 mg maximum)) + pyridoxine (B6) and rifapentine (RPT) (dose by weight) weekly for 3 mo
    - INH (5 mg/kg (300 mg maximum)) + pyridoxine (B6) daily for 9 mo (previous standard regimen, recommended when rifamycin regimens cannot be used)
    - INH (5 mg/kg (300 mg maximum)) + pyridoxine (B6) daily for 6 mo
    - INH (5 mg/kg (300 mg maximum)) + pyridoxine (B6) and RIF (10 mg/kg (600 mg maximum)) daily for 3 mo

TB Treatment

RIPE
Rifampin
INH
Pyrazinamide
Ethambutol

Treatment of Active Infection

- given the nuances of TB treatment, active TB infection should be managed by an experienced TB clinician

pulmonary TB: INH + rifampin + pyrazinamide + ethambutol x 2 mo (initiation phase), then INH + rifampin x 4 mo in fully susceptible TB (continuation phase), total 6 mo. Extend continuation phase to 7 mo if >65 y/o, pregnant, or risk of hepatotoxicity

- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- for patients taking INH, pyridoxine should be added in cases of diabetes, renal failure, malnutrition, substance use disorders, seizure disorders, pregnancy/breastfeeding, risk of neuropathy
- empiric treatment of suspected MDR or extensively drug-resistant (XDR) TB requires referral to a specialist
    - MDR = resistance to INH and rifampin ± others
    - XDR = resistance to INH + rifampin + fluoroquinolone + >1 of injectable, second-line agents
        - very difficult to treat, global public health threat, 5 documented cases in Canada from 1997-2008
    - suspect MDR TB if previous treatment failed, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Public Health Agency of Canada website for more information)

HIV and AIDS

Epidemiology

Canadian Situation (Public Health Agency of Canada, 2016)
- estimated 65040 Canadians living with HIV infection at the end of 2016, 20% unaware of HIV-positive status
- 2090 new infections were reported in 2013: MSM account for 53% of cases, people who inject drugs (PWID) 19%%

Global Situation (WHO and UNAIDS Core Epidemiology Slides, July 2018)
- estimated 36.7 million people living with HIV/AIDS at the end of 2016
- estimated 1.8 million newly infected in 2016
- estimated 1 million AIDS-related deaths in 2016

Etiology

- HIV is a retrovirus that causes progressive immune system dysfunction, predisposing patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17), and capsid (p24), enclosing 2 single-stranded copies of RNA plus enzymes in its core
- virion glycoproteins bind CD4 and CCR5/CXCR4 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by viral reverse transcriptase; dsDNA is integrated into host genome by viral integrase
- virus DNA transcribed and translated using host cell machinery, post-translational modifications include proteolytic activity of virally encoded protease enzymes
- newly produced virions bud out of host cell, incorporating host cell membrane; additional maturation steps are required before virion is considered infectious
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, and increased cell turnover

Modes of Transmission

Table 20. Modes of Transmission in Adolescents and Adults by Site and Medium

HIV Invasion Site	Sub-Location	Transmission Medium	Transmission Probability per Exposure Event
Female genital tract	Vagina, ectocervix, endocervix	Semen	1 in 200 to 1 in 2000
Male genital tract	Inner foreskin, penile urethra	Cervicovaginal and rectal secretions and desquamations	1 in 700 to 1 in 3000
Intestinal tract	Rectum	Semen	1 in 20 to 1 in 300
	Upper GI tract	Semen	1 in 2500
		Maternal blood/genital secretions (intrapartum)	1 in 5 to 1 in 10
		Breastmilk	1 in 5 to 1 in 10
Placenta	Chorionic villi	Maternal blood (intrauterine)	1 in 10 to 1 in 20
Blood stream		Contaminated blood products	95 in 100 to 1 in 150
		Sharp/needlestick injuries	

Adapted with permission from Macmillan Publishers Ltd., Hladik F, McElrath MJ. Setting the stage: host invasion by HIV. Nat Rev Immunol 2008;8:447-457.
NOTE: these estimates are for "all comers" i.e. they estimate transmission risk for anyone with HIV infection and do not take into account treatment status of the HIV+ person (in contrast to results of PARTNER study)

p24 = capsid protein
gp41 = fusion and entry
gp120 = attachment to host T-cell

Homozygosity for A32 mutation in CCR5 gene confers relative resistance to HIV infection
Heterozygosity for A32 mutation in CCR5 gene associated with slower disease course

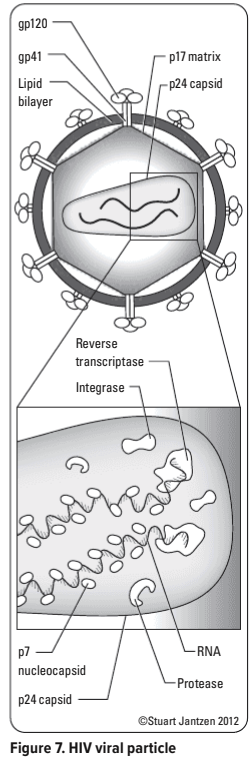


Figure 7. HIV viral particle

Natural History

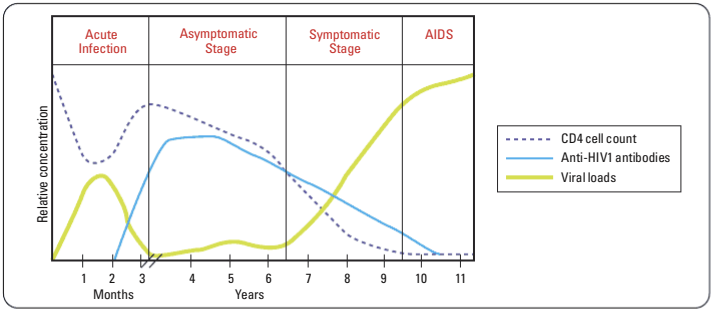


Figure 8. Relationships between CD4 T-cell count, viral load, and anti-HIV1 antibodies

Acute (Infection) Retroviral Syndrome

- 40-90% experience an acute non-specific illness (may include fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, headache, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis, CN palsies, or other neurological presentations; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high-risk of transmission

Asymptomatic (Latent) Stage

- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count in adults: 500-1100 cells/mm ^{3}
- CD4 count drops 60-100 cells/mm ^{3}per yr but is variable
- by 10 yr post-infection, 50% have advanced HIV (i.e. AIDS), 30% demonstrate milder symptoms, and <20% are asymptomatic if untreated

Definition of AIDS

- HIV-positive AND one or more of the clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. Pneumocystis jiroveci pneumonia (PJP, previously PCP), esophageal candidiasis, CMV, Mycobacterium avium complex (MAC), TB, toxoplasmosis), malignancy (Kaposi's sarcoma, invasive cervical cancer), wasting syndrome OR CD4 <200 (or <15%); this is largely historical because ART can reverse CD4 count decline

Table 21. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)

CD4 Counts	Possible Manifestations
<500 cells/mm^3	Often asymptomatic Constitutional symptoms: fever, night sweats, fatigue, weight loss Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), KS Recurrent bacterial infections, especially pneumonia Pulmonary and extrapulmonary tuberculosis Lymphoma
<200 cells/mm^3	*Pneumocystis jiroveci* pneumonia (formerly PCP) KS Oral thrush Local and/or disseminated fungal infections: *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*
<100 cells/mm^3	Progressive multifocal leukoencephalopathy (PML) – JC virus CNS toxoplasmosis
<50 cells/mm^3	CMV infection: retinitis, colitis, cholangiopathy, CNS disease MAC Bacillary angiomatosis (disseminated *Bartonella*) Primary CNS lymphoma (PCNSL)

Laboratory Diagnosis

- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo (therefore 3 mo window period)
- initial screening test (3rd generation antibody test): ELISA detects serum antibody to HIV; sensitivity >99.5%
- increasingly, combination p24 antigen/HIV antibody tests (4th generation) used for screening; improved sensitivity in early or acute infection and sensitivity/specificity approach 100% for chronic infection
- confirmatory test: if positive screen, Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160); specificity >99.99%

Sexual Activity without Condoms and Risk of HIV Transmission in Serodifferent Couples when the HIV-Positive Partner is using Suppressive Antiretroviral Therapy
JAMA 2016;316(2):171-181
Purpose: To evaluate the rate of within-couple HIV transmission (heterosexual and MSM) during periods of sex without condoms and when the HIV+ partner had HIV-1 RNA <200 copies/mL.
Methods: Prospective, observational PARTNER study, enrolled 1166 HIV serodifferent couples (in which the HIV+ partner was taking ART) who reported having condomless sex. Primary outcome was risk of within-couple HIV transmission to HIV- partner.
Results: Enrolled couples provided 1238 eligible couple-years of follow-up. Couples reported condomless sex for a median of 2 yr and condomless sex with other partners was reported by 108 HIV- MSM and 21 heterosexuals. While 11 HIV- partners became HIV+ (10 MSM; 1 heterosexual), no phylogenetically linked transmissions occurred over eligible couple-years of follow-up (within-couple HIV transmission = 0, 95% CI 0.30-0.71 per 100 couple-years).
Conclusions: Among serodifferent heterosexual and MSM couples in which HIV+ partner was using ART and who reported condomless sex, during median 1.3 yr/couple follow-up, there were no documented cases of within-couple transmission.

Seroconversion: Development of detectable anti-HIV antibodies

Window Period: Time between infection and development of anti-HIV antibodies; when serologic tests (ELISA, Western blot) are negative

All infants born to HIV-infected mothers have positive enzyme linked immunosorbent assay (ELISA) tests because of circulating maternal anti-HIV antibodies, which disappear by 18 mo; early diagnosis is made by detection of HIV RNA in plasma

HLA-B*5701 Testing
Abacavir hypersensitivity reactions usually only occur in individuals carrying this HLA allele (~5-7% of White individuals, lower prevalence in other ethnic groups)
Routine screening for HLA-B*5701 at baseline and definitely prior to abacavir use

HIV Status
CD4 count: progress and stage of disease
Viral load: rate of progression

HIV Non-disclosure Laws in Ontario
In 2017, Ontario changed HIV non-disclosure laws for people living with HIV, where non-disclosure of HIV status to a sexual partner is no longer considered a criminal offense if one of the following criteria is met:

- On antiretroviral therapy with a viral load <200 copies/mL for at least 6 mo
- Viral load between 200-1500 copies/mL and a condom is used properly and does not break

- rapid (point-of-care) antibody tests: higher false positives, therefore need to confirm positive results with traditional serology
- p24 antigen: detection by ELISA may be positive during "window period"

Management of the HIV-Positive Patient

- verify positive HIV test
- complete baseline history and physical exam, then follow-up every 3-6 mo
- laboratory evaluation
  - if non-stable and non-suppressed viral load, order routine CD4 count to measure status of the immune system
  - routine HIV-RNA levels (viral load) also important indicator of effect of ART
  - baseline HIV resistance testing to guide ARV therapy
  - HLA-B*5701 genetic test to screen for abacavir hypersensitivity if considering abacavir in treatment regimen
  - CCR5 tropism testing if considering CCR5 antagonist in treatment regimen
  - baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
  - baseline serologies (hepatitis A, B, and C, syphilis, toxoplasmosis, CMV, VZV)
  - routine biochemistry and hematology, CXR, urinalysis
  - annual fasting lipid profile and fasting glucose (due to ART side effects)
- education
  - regular follow-up on viral loads (q3-6 mo) as well as strict adherence to ART improves prognosis; routine monitoring of CD4 counts until consistently over 500 cells/mm^{3}with suppressed viral load
  - prevention of further transmission through safer sex and clean needles for IDU
  - HIV superinfection (transmission of different HIV strains from another HIV+ person) can rarely occur so barrier protection during sex is still recommended
  - discuss importance of disclosing HIV status to partners including risk of criminal prosecution of non-disclosure in jurisdictions where applicable
  - connect to relevant community groups and resources
- health care maintenance
  - assessment of psychosocial concerns and referral to psychiatry or social work if appropriate
  - vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative), HPV
  - annual screening (PAP smear), regular STI screening
  - management of comorbid conditions and provision of general primary care

Table 22. Prophylaxis Against Opportunistic Infections in HIV-infected Patients

Pathogen	Indication for Prophylaxis	Preferred Prophylactic Regimen
Pneumocystis jirovecii	CD4 count <200 cells/mm^3	TMP/SMX 1 SS or DS once daily
Toxoplasma gondii	IgG antibody to *Toxoplasma* and CD4 count <100 cells/mm^3	TMP/SMX 1 DS once daily
Mycobacterium tuberculosis	PPD reaction >5 mm or contact with case of active TB	INH + pyridoxine daily x 9 mo
***Mycobacterium* avium complex**	CD4 count <50 cells/mm^3	No prophylaxis if patients are started on ARTs

SS = single strength; DS = double strength
See USPHS/IDSA guidelines for preventing opportunistic infections among HIV-infected persons (Relevant Sections updated 2013, 2015). Available from: http://aidsinfo.nih.gov/

Anti-Retroviral Treatment

Overall Treatment Principles

- recommended that all HIV-positive patients initiate combination ART to restore and preserve immune function, reduce morbidity, prolong survival, and prevent transmission
- patients starting ART should be committed to treatment and understand the importance of adherence; poor compliance can lead to viral resistance; may defer treatment on the basis of clinical and psychosocial factors on case-by-case basis
- consider results of baseline resistance testing and complete ART history before initiating or re-initiating ART
- goal: keep viral load below limit of detection i.e. <20 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo, and restore immunological function
- strong evidence against intermittent ART or 'drug holidays'
- patient with undetectable viral load adhering to ART does not transmit HIV to sexual partners

ART Recommendations for Treatment of Naïve Patients

- 2 NRTIs + 1 INSTI or "boosted" PI (combined with ritonavir or cobicistat for improved pharmacokinetics)
- note: guidelines are subject to frequent change. Combination therapy is suggested, preferably with single pill regimens

Treatment Failure

- defined primarily by viral load (persistently >200 copies/mL)
- ensure that viral load >20 is not just a transient viremia or 'blip'; confirm medication adherence, assess drug interactions, perform resistance testing

1° and 2° prophylaxis may be discontinued if CD4 count is above threshold for ≥6 mo while on ART

Anti-Retroviral Pre-Exposure Prophylaxis for Preventing HIV in High-Risk Individuals
Cochrane DB Syst Rev 2012;7:CD007189
Purpose: To evaluate the efficacy of oral anti-retroviral prophylactic therapy in preventing HIV infection.
Study: Systematic review of 12 randomized controlled trials with 6 trials forming the core analysis.
Population: 9849 HIV-uninfected patients at high risk of contracting HIV including MSM, serodiscordant couples, and others.
Outcome: New infection with HIV.
Results: Daily oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) reduced the risk of HIV acquisition compared to placebo (RR 0.49; 95% CI 0.28-0.85). TDF alone also showed significant risk reduction in trials with fewer patients (RR 0.33; 95% CI 0.20-0.55). There was no significant increase in adverse events in any of the treatment groups. Sexual practices and adherence did not differ between treatment and placebo arms.
Conclusions: Pre-exposure prophylaxis with TDF with or without FTC effectively reduces the risk of HIV acquisition in high-risk, HIV-uninfected patients without causing significant adverse effects.

Reasons for Deterioration of a Patient with HIV/AIDS

- Opportunistic infections
- Neoplasms
- Medication-related toxicities
- Co-infections (e.g. HBV, HCV, STIs)
- Non-AIDS-related comorbidities (e.g. cardiovascular, renal, hepatic, neurocognitive, bone disease)

Treatment Failure

- Assess adherence
- Assess drug interactions
- Resistance testing
- Rule out opportunistic infections
- Rule out marrow suppression
- Construct new combination drug regimen

Table 23. Anti-Retroviral Drugs

Class	Drugs	Mechanism	Adverse Effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	abacavir (ABC) emtricitabine (FTC) lamivudine (3TC) tenofovir disoproxil fumarate (TDF) tenofovir alafenamide (TAF) zidovudine (AZT) didanosine (ddI) stavudine (d4T) **Combination Tablets:** AZT/3TC (Combivir®) AZT/3TC/ABC (Trizivir®) ABC/3TC (Kivexa®) TDF/FTC (Truvada®) TAF/FTC (Descovy®)	Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth	Lactic acidosis (often secondary to mitochondrial toxicity) Lipodystrophy Rash Nausea/vomiting/diarrhea Bone marrow suppression (AZT) Peripheral neuropathy (ddI, d4T) Drug-induced hypersensitivity (ABC) Pancreatitis (ddI/d4T) Myopathy (AZT)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	delavirdine (DLV) doravirine (DOR) efavirenz (EFZ) etravirine (ETR) nevirapine (NVP) rilpivirine (RPV)	Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication	Rash, Stevens-Johnson syndrome CNS: dizziness, insomnia, somnolence, abnormal dreams (EFZ) Hepatotoxicity (NVP – avoid in females with CD4 >250, men with CD4 >400) CYP3A4 interactions
Protease inhibitors (PIs)*	atazanavir (ATV) amprenavir (APV) darunavir (DRV) darunavir/cobicistat (DRV/c) lopinavir/ritonavir (LPV/r) nelfinavir (NFV) ritonavir (RTV) tipranavir (TPV) indinavir	Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins	Lipodystrophy, metabolic syndrome Nausea/vomiting/diarrhea Nephrolithiasis (indinavir) Rash (APV) Hyperbilirubinemia (ATV, indinavir) CYP3A4 interactions Hyperlipidemia
Integrase strand transfer inhibitors (INSTIs)	bictegravir cabotegravir dolutegravir (DTG) elvitegravir (EVG) raltegravir (RAL)	Inhibits integration of HIV DNA into the human genome thus preventing HIV replication	
Fusion inhibitor (only used if resistance)	enfuvirtide (T-20)	Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection	Injection site reactions, rash, infection, diarrhea, nausea, fatigue
CCR5 antagonist	maraviroc (MVC)	Inhibit viral entry by blocking host CCR5 co-receptor	Fever, cough, dizziness

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations

Lactic Acidosis

Occurs secondary to mitochondrial toxicity

Symptoms include abdominal pain, fatigue, nausea/vomiting, muscle weakness

Lipodystrophy

Body fat redistribution (mainly with old ARVs)

Lipohypertrophy (e.g. dorsal fat pad, breast enlargement, increased abdominal girth) thought to be caused primarily by protease inhibitors

Lipoatrophy (e.g. facial thinning, decreased adipose tissue in the extremities) is thought to be caused by thymidine analogue NRTIs such as d4T and AZT

Metabolic abnormalities: lipids (increased LDL, increased TGs), glucose (insulin resistance, T2DM), increased risk of CVD

Single Tablet ART Regimens

- reduces pill burden and increases adherence
- generally better tolerated

Table 24. Single Tablet ART Regimens

Name	Contents	Common Side Effects
Biktarvy®	bictegravir/emtricitabine/tenofovir alafenamide	good side effect profile
Genvoya®	tenofovir/emtricitabine/elvitegravir/cobicistat	good side effect profile
Complera®	rilpivirine/emtricitabine/tenofovir	good side effect profile
Odefsey®	rilpivirine/emtricitabine/tenofovir alafenamide	good side effect profile
Stribild®	elvitegravir/cobicistat/emtricitabine/tenofovir	good side effect profile
Triumeq®	dolutegravir/abacavir/lamivudine	good side effect profile; use only in HLAB*5701 negative patients
Atripla®	efavirenz/tenofovir/emtricitabine	psychiatric events, vivid dreams

Recommended ARV Regimens for Treatment-Naïve HIV-infected Adults

- initial regimens for treatment (most include an integrase inhibitor and a pair of NRTIs):
  1. bictegravir/TAF/FTC
  2. DTG/ABC/3TC (in patients confirmed to be HLB*5701 negative)
  3. DTG + (TAF or TDF)/(FTC or 3TC)
  4. raltegravir + TAF (or TDF)/FTC
  5. DTG/3TC
- note: not all regimens are available in all regions

Recommended ARV Regimens for Individuals of Childbearing Potential

- there is an increased risk of neural tube defects in infants born to women on dolutegravir at time of conception
- it is not known if other INSTIs also increase risk of neural tube defects
- therefore, before beginning an INSTI-containing treatment regimen in individuals of childbearing potential, the following should be considered:
  - completing a pregnancy test
  - a discussion on risks and benefits of dolutegravir, and lack of information on other INSTIs
  - for individuals attempting to conceive: RAL + TDF/FTC, TDF/3TC, or ABC/3TC are preferred regimens; DTG regimens to be used as an alternative only
  - for individuals not attempting to conceive but are sexually active and not using contraception, consider effectiveness/tolerability, patient preferences in decision
  - for individuals using effective contraception, treatment approach is similar to that of individuals in the general population with HIV

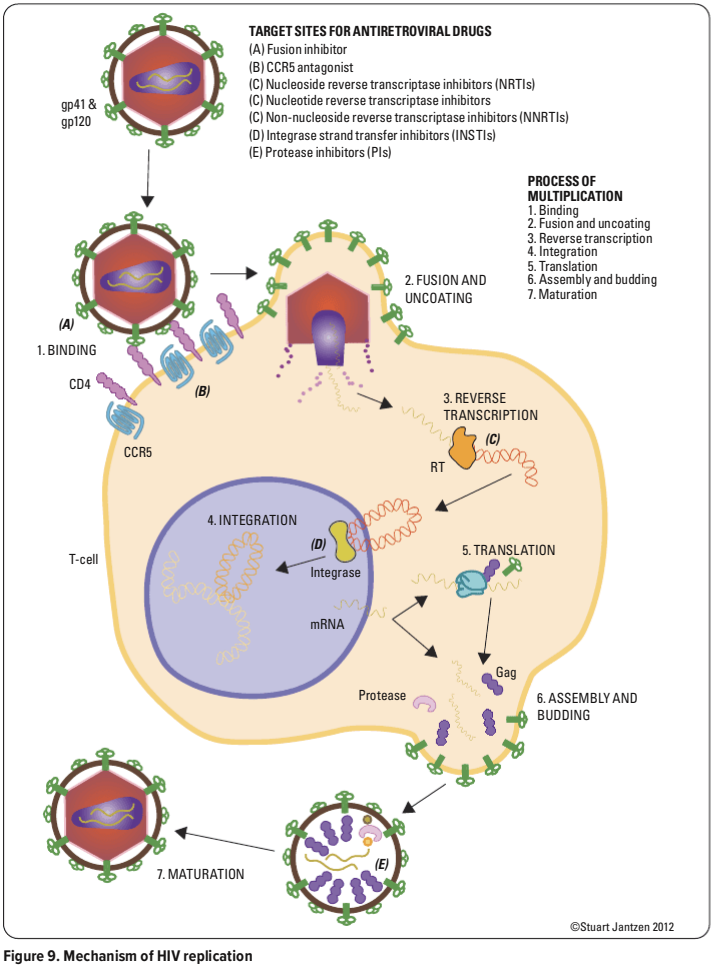


Figure 9. Mechanism of HIV replication

Prevention of HIV Infection

- education, including harm reduction
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm reduction for IVDU: avoid sharing needles
- prevention of vertical HIV infection: treatment with ART should be initiated prior to pregnancy or as early as possible during pregnancy. The risk of vertical HIV transmission can be reduced to <1% if maternal ART is started in a timely manner and the maternal viral load is undetectable prior to delivery
- universal blood and body precautions for healthcare workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV
  - PrEP strategies include daily TDF/FTC or TAF/FTC and "PrEP on demand", where medication is taken as a double dose 12-24 h before anticipated exposure and then for 2 more doses 24 and 48 h later (i.e. 2-1-1 dosing)
- ART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation

Early identification of HIV is essential for patients to receive the maximal benefit from ART

Efficacy, Safety, and Effect on Sexual Behaviour of On-Demand Pre-Exposure Prophylaxis for HIV in Men who have Sex with Men: An Observational Cohort Study
Lancet HIV 2017;4:402-410
Purpose: Assess the efficacy, safety, and effect of on-demand pre-exposure prophylaxis (PrEP) on sexual behaviour.
Methods: Men and transgender women who have sex with men, previously enrolled in the placebo-controlled ANRS IPERGAU trial. On demand tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) to be taken before and after sexual intercourse and participants assessed for incidence of HIV, PrEP adherence, safety, and sexual behaviour.
Results: HIV incidence was 0.19/100 person-years (95% CI 0.01-1.08) vs. 6.60/100 person-years (95% CI 3.60-11.05) in the placebo group, relative risk reduction of 97%. Drug-related GI events were reported in 14% of participants but were self-limiting. Participants reporting condomless sex at their last receptive anal intercourse increased from 77 to 86% at 18 mo follow-up.
Conclusions: On-demand oral PrEP is highly effective at preventing HIV infection among high-risk MSM. This represents an alternative to daily PrEP.

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women
NEJM 2016;375:2121-2132
Purpose: To evaluate whether longer-acting methods of anti-retroviral therapy (i.e. vaginal rings) may simplify use of medications and provide HIV-1 protection.
Methods: Phase 3, randomized, double-blind, placebo-controlled trial of monthly vaginal ring containing dapivirine in women (aged 18-45) in Malawi, South Africa, Uganda, and Zimbabwe.
Results: Among 2629 women enrolled, the incidence of HIV-1 infection was 3.3/100 person-years in dapivirine group and 4.5/100 person-years in placebo group. Post hoc analysis identified higher rates of HIV-1 protection in women >21 yr (56%, 95% CI 31-71) but not among those <21 yr (-27%, 95% CI -133-31), which correlated with reduced adherence.
Conclusions: Monthly vaginal ring containing dapivirine reduced risk of HIV-1 infection among African women.

Types of Testing

1. Nominal/Name-Based HIV Testing
- person ordering the test knows the identity of the person being tested for HIV
- HIV test is ordered using the name of the person being tested
- person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
- test result is recorded in the healthcare record of the person being tested

2. Non-Nominal/Non-Identifying HIV Testing
- similar to nominal/name-based testing on all points except:
  - HIV test is ordered using a code or the initials of the person being tested

3. Anonymous Testing
- available at specialized clinics
- person ordering the HIV test does not know the identity of the person being tested
- HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
- test results are not recorded on the healthcare record of the person being tested
- patient identification and notification of Public Health required to gain access to ART

HIV Pre- and Post-Test Counselling

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV-positive individuals should be connected with local support services

FUNGAL INFECTIONS

Skin and Subcutaneous Infections

Superficial Fungal Infections

- see Dermatology, D32, D33, D37, D45 D46, and D49

Dermatophytes

- see Dermatology, D31

Subcutaneous Fungal Infections

Etiology
- subcutaneous inoculation by fungi that naturally reside in the soil, including *Sporothrix schenckii*, which usually occurs in gardeners injured by a rose thorn or splinter

Clinical Features
- causes subcutaneous nodules at the point of entry, may develop into an ulcer
- fungi may migrate up lymphatic vessels creating nodules along the way – "nodular lymphangitis"

Treatment
- oral azole
- IV amphotericin B for severe or disseminated infection

Endemic Mycoses

Etiology

- fungal infection that occurs through the inhalation of spores (from soil, bird droppings, vegetation) or inoculation injury
- thermally dimorphic organisms: mould in cold temperature (e.g. soil), and yeast at higher temperature (e.g. tissue)
- in North America, the three major endemic mycoses are: histoplasmosis, blastomycosis, and coccidioidomycosis
- NB. Previously defined regions of endemicity are expanding and can no longer be used to definitively rule out infections with specific organisms

Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts, and bat caves

Clinical Features

- may be asymptomatic
- all can cause pneumonia and may disseminate hematogenously
- may reactivate or disseminate during immunocompromised states

Table 25. Endemic Mycoses

Disease	Endemic Region	Clinical Features	Investigations
Histoplasma capsulatum	Ohio and Mississippi River valleys in central USA, Ontario, Quebec; widespread	Asymptomatic (in most people) Primary pulmonary Fever, cough, chest pain, headache, myalgia, anorexia CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy CXR (chronic): pulmonary infiltrates, cavitary disease Disseminated (rare) Occurs primarily in immunocompromised patients Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS	Fungal culture, fungal stain Antigen detection (urine and serum) Serology
Blastomyces dermatitidis	States east of Mississippi River, Northern Ontario, and along the Great Lakes	May be asymptomatic Primary: acute or chronic pneumonia Fever, cough, chest pain, chills, night sweats, weight loss CXR (acute): lobar or segmental pneumonia CXR (chronic): lobar infiltrates, fibronodular interstitial disease Disseminated Spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), genitourinary tract (prostatitis, epididymitis)	Sputum smear and culture Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material)
Coccidioides immitis	Deserts in southwest USA, northwest Mexico	"Valley fever": subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for wk to mo Can develop hypersensitivity with arthralgias, erythema nodosum Disseminated Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis) Common opportunistic infection in patients with HIV	Sputum culture Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material)

Opportunistic Fungi

Pneumocystis jirovecii (formerly *P. carinii*) Pneumonia: PJP or PCP

Etiology

- respiratory exposure to unicellular fungus (previously classified as a protozoan)
- can be transmitted from person to person
- without prophylaxis, HIV-positive patients with a CD4 count <200 cells/mm3 have an 80% lifetime risk of PJP
- most cases of PJP occur in patients who are unaware of their HIV infection, do not seek medical care for HIV, or who do not use prophylaxis
- in HIV-negative patients, PJP occurs almost exclusively in immunocompromised patients (e.g. organ transplant patients, inflammatory conditions, hematological malignancies)

CXR in *P. jirovecii*
Bilateral, diffuse opacities
CXR may be normal (20-30% cases)
CT shows cysts (hence the name Pneumocystis) but almost never pleural effusions

Clinical Features

- symptoms of pneumonia: fever, non-productive cough, progressive dyspnea (and hypoxia)
- classic CXR findings of interstitial pneumonia
- most clinical disease is due to reactivation of latent infection or reinfection by a different genotype in immunocompromised patients (steroid use, HIV)

Investigations

- CXR: bilateral symmetrical interstitial infiltrates
- ABG: reduced pO_2 and elevated alveolar-arterial (A-a) gradient
- serum LDH: elevated (>220 IU/L)
- induced sputum or lower airway sampling: positive for Pneumocystis, traditional test was immunofluorescence however many labs using quantitative PCR

Treatment and Prevention
- oxygen to keep SaO_2 >90%
- antimicrobial options
  - TMP/SMX (PO or IV) is preferred therapy, even for those taking this for prophylaxis
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV) is second line in severe disease
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia (pO_2 <70 mmHg or A-a gradient O_2 >35 mmHg)
- prophylactic TMP/SMX for those at high-risk of infection (HIV patients when CD4 <200 cells/mm^3 or non-HIV immunocompromised patients under specific conditions)

Cryptococcus spp.

Etiology
- inhalation of airborne encapsulated yeast from soil contaminated with pigeon droppings (*C. neoformans*) or certain tree species such as Eucalyptus or Douglas fir (*C. gatti*)
- *C. neoformans* tends to affect immunocompromised hosts vs. *C. gatti* which tends to affect immunocompetent hosts

C. gattii has a limited geographical distribution including Vancouver Island, Northern Australia, and Papua New Guinea

Clinical Features
- asymptomatic
- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of *Molluscum contagiosum*
  - other: bone, lymph nodes, bone marrow, soft tissues, eyes, prostate

Investigations
- serum cryptococcal antigen
- CSF for meningitis: India-ink stain or cryptococcal antigen test, culture to confirm
- lateral flow cryptococcal antigen assay from serum and CSF
- LP with measurement of opening pressure

India-ink sensitivity for Cryptococcus is only 50% (higher in HIV patients); now replaced by cryptococcal antigen test in most laboratories

Treatment
- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance
  - serial lumbar puncture or other method of managing increased ICP an important adjunct to therapy

Candida albicans

Etiology
- overgrowth of *C. albicans* (normally found as part of the microbiome of the skin, mouth, vagina, and GI tract)
- risk factors for overgrowth:
  - immunocompromised state (DM, corticosteroids)
  - critically ill patients (broad-spectrum antibiotic use, central venous catheters, total parenteral nutrition)
  - obesity: maceration and moisture in intertriginous areas, pannus, under breasts

Clinical Features
- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY26), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease

Treatment
- thrush: clotrimazole troches, miconazole mucoadhesive buccal tablets, or nystatin suspension or pastilles for mild disease, fluconazole for severe or refractory disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

Aspergillus spp.

Etiology
- infection with *Aspergillus* fungi (*A. fumigatus*, *A. flavus*) which is found ubiquitously in the air and the environment
- *Aspergillus* produces a toxin called aflatoxin that contaminates nuts, grains, and rice

Clinical Features
- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a pre-existing lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia or transplantation
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, cavitation; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules with surrounding ground glass ("halo" sign)
- mycotoxicosis
  - aflatoxin produced by *A. flavus* (nuts, grains, rice)
  - results in liver hemorrhage, necrosis, and hepatocellular carcinoma formation

Treatment Options
- voriconazole or amphotericin B for invasive aspergillosis
- surgical resection for aspergilloma; a bronchial artery embolization for severe hemoptysis due to erosion of bronchial arteries from aspergilloma
- corticosteroids ± itraconazole for ABPA

See Landmark Infectious Disease Trials table for more information on the voriconazole vs. amphotericin B for invasive aspergillosis trial. It compared voriconazole with amphotericin B for primary therapy of invasive aspergillosis.

PARASITIC INFECTIONS

Protozoa – Intestinal/Genitourinary Infections

Entamoeba histolytica (Amoebiasis)

Etiology
- infection with *E. histolytica* occurs when the cysts are transmitted via the oral-fecal route in areas of poor sanitation that have been contaminated by other infected humans, or via sexual activity
- seen in migrants, travellers, institutionalized individuals, Indigenous peoples, MSM

Clinical Features
1. asymptomatic carriers
2. amoebic dysentery
   - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction, and ulceration of large intestine
3. amoebic abscesses (liver abscesses, see General and Thoracic Surgery, GS52)
   - most common in liver (hematologic spread); presents with right upper quadrant pain, weight loss, fever, hepatomegaly
   - can also occur in lungs and brain

Investigations
- serology, fecal/serum antigen testing, stool microscopic exam (for cysts and trophozoites), colon biopsy, single stool for multiplex enteric parasite PCR
- *E. histolytica* indistinguishable microscopically from the non-pathogenic *E. dispar* (distinguish by specific stool antigen detection or multiplex stool PCR assay)

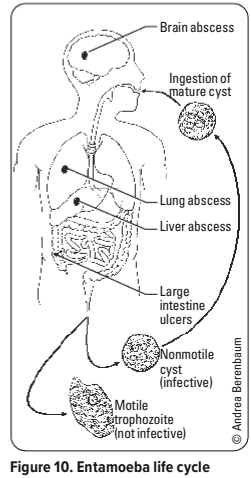


Figure 10. Entamoeba life cycle

Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of abscess rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst shedding: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)

Giardia lamblia

Etiology
- infection with G. lamblia occurs via the fecal-oral route with the ingestion of cysts from water/food contaminated by infected humans and other mammals (especially in the Rockies)
- risk factors: travel, camping, institutions, daycare centres, MSM

Clinical Features
- giardiasis ("beaver fever")
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats the small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucous in stool

Investigations
- multiple stool samples (daily x 3 d) for microscopy; single stool for multiplex enteric parasite PCR; stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

Treatment and Prevention
- metronidazole; nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

Trichomonas vaginalis

Etiology
infection with *T. vaginalis* occurs via sexual contact

Trichomonas causes 25% of vaginitis

Clinical Features
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- *Trichomonas* vaginitis (see Gynecology, GY26)
- vaginal discharge (profuse, malodorous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

Investigations
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

Treatment
- metronidazole for patient and partner(s)

Cryptosporidium spp.

Etiology
- infection with Cryptosporidium spp. via the fecal-oral route occurs with the ingestion of cysts from water contaminated by infected humans and other animals (including cows)
- risk factors: summer and fall, young children (daycare), MSM, contact with farm animals, immunodeficiency

Clinical Features
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with nausea/vomiting, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)

Investigations
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody, single stool for multiplex enteric parasite PCR

Treatment and Prevention
- supportive care
- in HIV+ patients, (re)initiate ART and try to increase their CD4 count to >100; if fails, try nitazoxanide or macrolides
- good personal hygiene, water filtration

Blood and Tissue Infections

Plasmodium spp. (Malaria)

Etiology

- transmission of *Plasmodium* spp. (*P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi*) primarily occurs during the blood meal of an infected female Anopheles mosquito
- sporozoites injected during the blood meal then infect human liver cells, where they multiply and are released as merozoites; merozoites infect red blood cells and cause disease
- infection with malaria parasites can also occur via vertical transmission (rare) or blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

Clinical Features

- flu-like prodrome (may include fever, chills, fatigue, diaphoresis, cough, rash, arthralgias, myalgias, headache, GI symptoms)
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of red blood cells) that can last several hours
  - *P. vivax* and *P. ovale*: chills and fever x 48 h but can be variable
  - *P. malariae*: chills and fever x 72 h but can be variable
  - *P. falciparum*: less predictable fever interval, can be highly variable
- abdominal pain, diarrhea, myalgia, headache, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis
- >90% of patients infected with *P. falciparum* are ill within 30 d
- relapsing malarial attacks may occur after many months due to the reactivation (entering the erythrocytic cycle) of dormant liver hypnozoites of either *P. ovale* or *P. vivax*
- complications:
  - *P. falciparum* (most common and most lethal): CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute kidney injury, ARDS, primarily responsible for fatal disease
  - *P. knowlesi*, and rarely *P. vivax*, can be fatal

Investigations

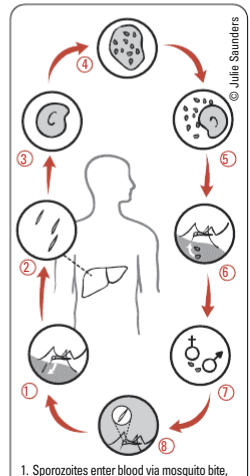
- CBC screen (assess for triad of: thrombocytopenia, elevated LDH, and anemia)
- microscopy: blood smear q12-24 h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests
- PCR

Treatment and Prevention

- all spp. of malaria can lead to severe infection *(P. falciparum* most likely to cause severe disease and death)
  - markers of severity: clinical features + parasitemia
  - in any patient with clinical evidence of severe disease: parenteral treatment (artemisinin combination therapy)
- *P. falciparum*: most areas of the world show chloroquine resistance – check local resistance patterns
  - artemisinin combination therapy (e.g. artesunate + doxycycline or artemether-lumefantrine)
  - atovaquone/proguanil combination (Malarone®)
  - quinine + doxycycline or clindamycin
  - mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- *P. vivax, P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: atovaquone/proguanil + primaquine or quinine and doxycycline + primaquine
- *P. malariae, P. knowlesi*: chloroquine
- prevention with antimalarial prophylaxis (although quality may vary regionally), covering exposed skin, insecticide-treated bed nets, insect repellent
- prevention of relapse for *P. vivax*: primaquine or the newly FDA-licensed tafenoquine (in patients ≥16 yr who are receiving appropriate antimalarial therapy for acute P. vivax infection)

Mefloquine for Preventing Malaria during Travel to Endemic Areas
Cochrane DB Syst Rev 2017;CD006491
Purpose: To summarize efficacy and safety of mefloquine used as prophylaxis for malaria in travellers.
Methods: Randomized control trials (for efficacy and safety) and non-randomized cohort studies (for safety) to compare prophylactic mefloquine with placebo, no treatment, or alternative antimalarial agent.
Results: Participants were more likely to discontinue mefloquine (6%) vs. atovaquone-proguanil (3%) due to adverse effects (including nausea, vomiting, abnormal dreams, insomnia, anxiety, and depressed mood during travel). No difference in serious adverse effects or discontinuation due to adverse effects was found between mefloquine and doxycycline or mefloquine and chloroquine.
Conclusions: Absolute risk of malaria during short-term travel appears low with mefloquine, doxycycline, and atovaquone-proguanil therapy. Choice of agent depends on how individual travellers assess importance of specific adverse effects, pill burden, and cost.

Malaria is the most common fatal infectious disease worldwide



1. Sporozoites enter blood via mosquito bite, infect liver
2. Hepatic infiltration
3. Infect red blood cells
4. Trophozoite divides asexually many times to produce schizont (contains merozoites)
5. Red blood cell lyses and merozoites attack other red blood cells (chills and fever)
6. Male and female gametocytes (from merozoites) ingested by mosquito during bite
7. Male and female gametocytes (from merozoites) fuse in mosquito gut; produce ookinete
8. Ookinete matures into an oocyst which contains individual sporozoites; migrates to mosquito salivary glands

Figure 11. Life cycle of *Plasmodium* spp.

Trypanosoma cruzi

Etiology
- found in Mexico, South America, and Central America
- transmission by reduviid insect vector ("Kissing Bug"), which defecates on skin and trypomastigotes in the stool are rubbed into bite site or intact mucous membranes by host
- trypomastigotes can penetrate intact buccal mucosa when orally inoculated (e.g. via sugar cane-sweetened unpasteurized juices)
  - also transmitted via placental transfer, organ transplantation, blood transfusion, and ingestion of food or drink contaminated by an infected triatomine
  - congenital acquisition increasingly recognized as a risk factor for Chagas disease being detected in non-endemic areas

Clinical Features
- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation (Chagoma) with variable fever, lymphadenopathy, cardiomegaly, and hepatosplenomegaly
  - if inoculation via conjunctiva: "Romana's sign;" usually unilateral
  - acute myocarditis, pericardial effusion, meningoencephalitis in severe cases
  - chronic indeterminate phase: asymptomatic but increasing levels of antibody in blood; most infected persons (60-70%) remain in this phase, and do not go on to manifest a determinate form of Chagas disease
  - chronic determinate: leads to chronic dilated cardiomyopathy, esophagomegaly, and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

Investigations
- wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

Treatment and Prevention
- acute: benznidazole or nifurtimox
- indeterminate: increasing trend to treat as acute infection for children and adults under age 50
- chronic determinate: symptomatic therapy, surgery as necessary including heart transplant, esophagectomy, and colectomy; there is unlikely a clinical benefit to antiparasitic treatment at the determinate stage of disease
- insect control, bed nets

Toxoplasma gondii

Etiology
- infection with *T. gondii* occurs through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), transplacental transmission, organ transplantation, gardening without gloves (cat oocyst exposure), whole blood transfusions, contaminated water sources

Clinical Features
- congenital
  - result of acute primary infection of mother during pregnancy (TORCH infection)
  - stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult- blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
- acquired
  - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
  - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (headache and focal neurological signs)
  - lymph node, liver, spleen enlargement, and pneumonitis
  - chorioretinitis

Investigations
- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination

Treatment and Prevention
- no treatment if: immunocompetent, not pregnant, no severe organ damage
- immunocompromised: pyrimethamine + sulfadiazine + folinic acid
- pregnancy: spiramycin if fetal status unknown, pyrimethamine + sulfadiazine + folinic acid if confirmed or highly suspected fetal infection, avoid undercooked meat and refrain from emptying cat litter boxes
- HIV: TMP/SMX
- proper hand hygiene, cook meat thoroughly to proper temperature

See Landmark Infectious Disease Trials table for more information on the BENEFIT trial. It details the role of trypanocidal therapy in patients with established Chagas cardiomyopathy.

Classic Triad of Congenital Toxoplasmosis
Chorioretinitis
Hydrocephalus
Intracranial calcifications

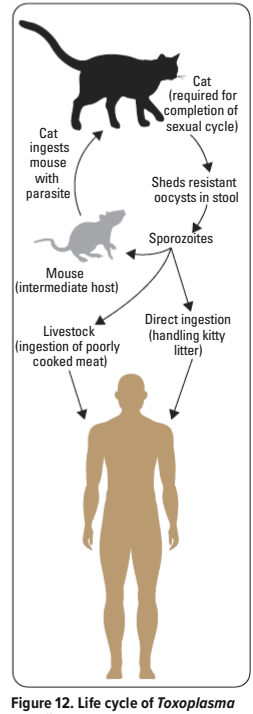

Cat
(required for completion of sexual cycle)
Sheds resistant oocysts in stool
Sporozoites
Direct ingestion (handling kitty litter)
Livestock (ingestion of poorly cooked meat)
Mouse (intermediate host)
Cat ingests mouse with parasite

Figure 12. Life cycle of *Toxoplasma gondii*

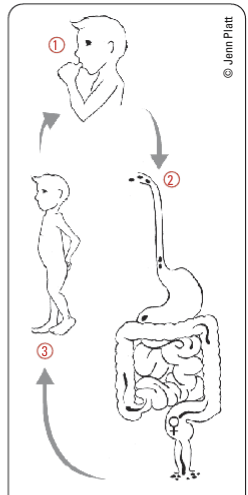
1/3 of Ontario's population is infected with *Toxoplasma gondii*

Helminths

Roundworms – Nematodes

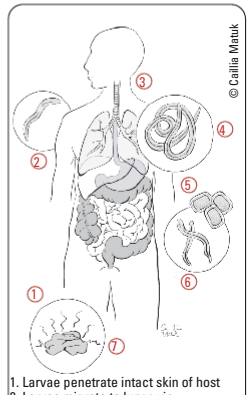
Table 26. Nematodes (Roundworms)

Nematode	Epidemiology	Transmission	Clinical Presentation	Management
Ascaris lumbricoides	Worldwide (most common in tropical and subtropical areas)	Human feces, ingestion of contaminated food or water containing eggs	Often asymptomatic, abdominal discomfort Heavy infections may cause intestinal blockage, growth impairment Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löffler's syndrome)	Mebendazole OR albendazole OR pyrantel pamoate OR ivermectin
Trichuris trichiura (whipworm)	Worldwide (most common in tropical areas)	Ingestion of eggs in soil	Diarrhea (± mucous, blood), abdominal pain, rectal prolapse, stunted growth	Mebendazole OR albendazole
Onchocerca volvulus	Sub-Saharan Africa, Latin America	Blackfly bite	River blindness (onchocerciasis), dermatitis	Ivermectin + doxycycline
Wuchereria bancrofti	Tropics	Mosquito bite	Damage to lymphatics causes lymphadenopathy, lymphedema, lymphatic filariasis (elephantiasis), hydrocele Tropical pulmonary eosinophilia	Diethylcarbamazine + doxycycline
Loa loa	West and Central African rainforest (e.g. Cameroon, Central African Republic)	Deerfly bite	Loiasis mostly asymptomatic. Can have episodic angioedema (Calabar swellings), eye pain and itching from subconjunctival migration	Surgical removal of adult worms, diethylcarbamazine, albendazole
Enterobius vermicularis (pinworm)	Worldwide	Human host: fecal-oral self-inoculation and fomite person-to-person transfer Adult worms live in cecum and deposit eggs in peri-anal skin	Asymptomatic carriers or severe nocturnal peri-anal itching (pruritus ani) Occasional vaginitis, ectopic migration to appendix or other pelvic organs Abdominal pain, nausea/vomiting with high worm burden	Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out) Examination of perianal skin at night may reveal adult worms Usually no eosinophilia as no tissue invasion Mebendazole, albendazole; pyrantel in pregnancy Change underwear, bathe in morning, pajamas to bed, wash hands, trim fingernails Treat all family members simultaneously Reinfection common
Strongyloides stercoralis (threadworm)	Subtropical, tropical, and temperate (including southern US)	Fecal contamination of soil: transmission via unbroken skin, walking barefoot Autoinfection: penetration of larvae through GI mucosa or perianal skin Adult worms live in mucosa of small intestine	One of few worms able to multiply in human host Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löffler's syndrome) Abdominal pain, diarrhea, pruritus ani, larva currens (itchy rash) Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; immunoablative therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection	Ivermectin and/or albendazole



1. Embryonated eggs ingested by humans
2. Larvae hatch in small intestine
3. Females migrate out anus at night

Figure 13. Life cycle of Enterobius



1. Larvae penetrate intact skin of host
2. Larvae migrate to lungs via bloodstream
3. Larvae crawl up trachea and down to GI tract (cough/swallow)
4. Adult worms in intestine
5. Eggs produced in bowel
6. Larvae
7. Bowel movement containing larvae

Figure 14. Life cycle of Strongyloides

Flatworms – Cestodes/Trematode

Table 27. Cestodes/Trematodes (Flatworms)

	Epidemiology	Transmission	Clinical Presentation	Treatment
CESTODES				
***Taenia solium* (pork tapeworm)**	Worldwide, but more common in places with poor sanitation	Undercooked pork (larvae), human feces (eggs)	Taeniasis: mild GI symptoms Cysticercosis: mass lesions in CNS, eyes, skin, seizures	Corticosteroids + albendazole + praziquantel for most cysticercosis Antiepileptics if seizures Praziquantel for taeniasis
***Taenia saginata* (beef tapeworm)**	Worldwide, but more common wherever contaminated raw beef is eaten	Undercooked beef (larvae)	Taeniasis: mild GI symptoms	Praziquantel
Diphyllobothrium latum	Europe, North America, Asia	Raw fish	Vitamin B_{12} deficiency leading to macrocytic anemia and posterior column deficits	Praziquantel
Echinococcus granulosus	Rural areas, sheep-raising countries	Dog feces (eggs)	Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture) Risk of anaphylaxis if cystic fluid released during surgical evacuation	Albendazole ± praziquantel alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole
TREMATODES				
Clonorchis sinensis	Japan, Taiwan, China, Southeast Asia	Raw fish	Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma	Praziquantel
Schistosoma spp.	Africa, Southeast Asia, focal in Western Hemisphere	Fresh water exposure	Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, squamous cell carcinoma (SCC) of the bladder)	Praziquantel

Schistosoma spp.

Etiology

infection with Schistosoma spp. (*S. mansoni, S. haematobium, S. japonicum*) occurs following penetration of unbroken skin by their larvae (cercariae) which are found in infested fresh water

- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- schistosomes cannot multiply in or pass between humans
- more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa

Clinical Features

- most asymptomatic; symptoms seen in travellers (nonimmune)
- swimmer's itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, headache, weight loss, cough, abdominal pain, chronic diarrhea, high-grade eosinophilia
- chronic schistosomiasis (can persist for years):
  - *S. mansoni, S. japonicum*
  - worms in mesenteric vein, eggs in portal tracts of liver and bowel
  - heavy infections: intestinal polyps, portal and pulmonary HTN, splenomegaly (2° to portal HTN), hepatomegaly
  - *S. haematobium*
    - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
    - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
  - neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
  - pulmonary complications: granulomatous pulmonary endarteritis, pulmonary HTN, cor pulmonale; especially in patients with hepatosplenic involvement

Investigations

- serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia), loop-mediated isothermal amplification, circulating serum antigen test
- *S. mansoni, S. japonicum*: eggs in stool, liver U/S shows peri-portal fibrosis, rectal biopsy
- *S. haematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

Treatment and Prevention

- praziquantel
- add prednisone if acute schistosomiasis or neurologic complications develop
- proper disposal of human waste, molluscicide (pesticide against molluscs), avoidance of infested fresh water while travelling

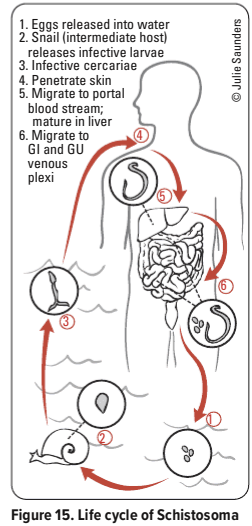

1. Eggs released into water
2. Snail (intermediate host) releases infective larvae
3. Infective cercariae
4. Penetrate skin
5. Migrate to portal blood stream; mature in liver
6. Migrate to GI and GU venous plexi
© Julie Saunders

Figure 15. Life cycle of Schistosoma

Ectoparasites

- scabies, lice
- see Dermatology, D33

Table 28. Important Exposures

Insect Bites	
Mosquito	*Plasmodium* spp. (malaria) Dengue Chikungunya *Wuchereria bancrofti* (lymphatic filariasis, aka elephantiasis) West Nile encephalitis Yellow Fever Japanese encephalitis Zika
Tick	*Borrelia burgdorferi* (Lyme disease) *Rickettsia rickettsii* (Rocky Mountain spotted fever)
Fly	*Trypanosoma brucei* spp. (human African trypanosomiasis (HAT), aka African sleeping sickness) *Leishmania* spp. (Leishmaniasis) *Bartonella bacilliformis* (bartonellosis)
Flea	*Yersinia* (Plague) *Tunga penetrans* (Tungiasis)
Mammal Bites	
Dog/Cat	Rabies, Pasteurella, anaerobes, *Streptococcus* spp., *S. aureus*, *Bartonella henselae*, *Clostridium tetani* (tetanus)
Human	*Streptococcus* spp., *S. aureus*, oral anaerobes, *Eikenella* spp.
Oral Exposures	
Unpasteurized Milk	*Brucella* spp., non-tuberculous Mycobacteria, *Salmonella* spp., *E. coli*, *Listeria* spp.
Undercooked Meat/Fish	Enteric bacteria, helminths, protozoa (e.g. Toxoplasma)
Water	Hepatitis A/E, norovirus, V. cholerae (cholera), *Salmonella*, *Shigella*, *Giardia*, poliovirus, *Cryptosporidium*, *Cyclospora*
Environmental Exposures	
Fresh Water	*Leptospira* spp., *Schistosoma* spp., *Acanthamoeba*, *Naegleria fowleri*
Soil	Hookworms, *Toxocara* spp. (visceral larva migrans), *Leptospira interrogans* (leptospirosis)

Adapted with permission from Lancet 2003;361:1459-1469

Travel Medicine

General Travel Precautions

- vector-borne: long sleeves, long pants, hats, insecticides (containing permethrin) applied to clothes, belongings, and bed nets; and skin repellents (e.g. DEET, icaridin) applied to exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (e.g. Lake Malawi), fresh-water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller's diarrhea (bismuth salicylate, rifaximin)
- standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio, influenza)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

Infectious Diseases to Consider

- vector-borne: malaria, dengue fever, chikungunya, yellow fever, spotted fever rickettsioses, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, leishmaniasis, Zika virus, filariasis
- sexually transmitted: HIV, HBV, acute HSV, syphilis, usual STIs, e.g. gonorrhea and chlamydia
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis, Ebola
- airborne: TB, measles, varicella
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amoebiasis, dysentery, traveller's diarrhea, cholera, *Campylobacter* spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

Fever in the Returned Traveller

Etiology

- commonly identified causes of fever in the returned traveller
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: typhoid from Salmonella (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller's diarrhea (10-20%), respiratory tract infection (10-15%), UTI/STI (2-3%)
  - Fever in a returned traveller from a malaria endemic area is considered malaria until proven otherwise
- can be caused by routine infections that are common in non-travellers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes (e.g. DVT/PE, drug fever, inflammatory disorder unmasked by travel-acquired infection)

History

- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
- persons visiting friends and family are more likely to be exposed to local population and pathogens
  - style of travel: lodgings, camping, adventure travelling
  - local population: sick contacts
  - transportation: use of animals
- exposure history
  - street foods, untreated water: increased risk of traveller's diarrhea, enteric fever
  - uncooked meat/unpasteurized dairy: increased risk of parasitic infection
  - body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  - increased risk of HBV, HCV, HIV, GC, *C. trachomatis*, syphilis
  - animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies
- fever pattern
- incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  - <21 d: consider malaria, typhoid fever, dengue fever, chikungunya, Zika, rickettsioses, traveller's diarrhea, respiratory tract infections (e.g. ILI, COVID-19); exclude HBV, TB
  - >21 d: consider malaria, TB, typhoid fever; exclude dengue fever, chikungunya, traveller's diarrhea, rickettsioses
- body systems affected: GI, respiratory, CNS, skin

Investigations

- all travellers with fever should undergo the following tests
  - blood work: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  - urine: urinalysis, urine C&S if dysuria or other localizing signs
- special tests based on symptoms, exposure history, and geography
  - stool: C&S, O&P
  - CXR
  - viral serology (hepatitis, HIV)
  - dengue serology for IgM, dengue PCR

Treatment

- empiric treatment if ongoing fever for 48-72 h and negative malaria smears and all cultures pending
- travelled to India, Southeast Asia: azithromycin ± doxycycline
- travelled elsewhere: ciprofloxacin ± doxycycline

Table 29. Fever in the Returned Traveller

Illness	Geography/ Timing	Pathogen	Incubation Period	Clinical Manifestations	Diagnosis	Treatment
Malaria	Africa, India, Central and South America, Southeast Asia Usually rural, night-biting mosquitoes	*P. falciparum* *P. vivax* *P. malariae* *P. ovale* *P. knowlesi*	7-30 d to mo or yr	Fever and flu-like illness (shaking chills, headache, muscle aches, and fatigue) Nausea/vomiting and diarrhea Anemia and jaundice *Plasmodium falciparum*: (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure	Blood smear (thick and thin) x3 Rapid diagnostic test (with smear or PCR confirmation) Antigen detection PCR	Artesunate (for severe disease) + Malarone®, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine
Dengue	Southeast Asia, Caribbean Usually urban, day-biting mosquitoes	Dengue viruses 1-4	3 d to 2 wk	Sudden onset of fever, headache, retro-orbital pain, myalgias, and arthralgias Leukopenia Thrombocytopenia hemorrhagic manifestations (rare in travellers)	Anti-dengue IgM positivity PCR	Symptom relief: acetaminophen (avoid using NSAIDs and ASA because of antiplatelet properties)
Typhoid (enteric fever)	Global but mostly Indian subcontinent	*Salmonella enterica* serotype *Typhi* or serotype *Paratyphi*	3 to 60 d	Sustained fever 39°-40°C (103°-104°F) Abdominal pain, headache, loss of appetite, cough, constipation	Stool, urine, or blood culture positive for *S.* ser. Typhi or S. ser. Paratyphi	Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone, or macrolide
Tick Typhus	Mediterranean, South Africa, India	*Rickettsia*	1 to 2 wk	Fever, headache, myalgia, spotted rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes	Serology Presence of classic tick eschar	Doxycycline
TB	Global	*M. tuberculosis*	Variable	Fever, cough, hemoptysis	CXR Sputum culture and acid-fast stain Nucleic Acid Amplification Test (NAAT)	Isoniazid (INH), rifampin (RIF), Pyrazinamide (PZA), Ethambutol (EMB) + Vitamin B6
Mononucleosis	Caribbean, Central and South America	EBV or CMV	30 to 50 d	Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly	Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test	Acetaminophen or NSAIDs, fluids
Zika Virus Disease	Africa, Southeast Asia, South America; spreading	Zika virus	Unknown, likely 3 to 12 d	Headache, malaise, myalgia, arthralgia, mild fever, rash, conjunctivitis	RT-PCR Serology	Rest, fluids, analgesics/ antipyretics (avoid NSAIDs until dengue ruled out), condom use, avoid pregnancy

Fever of Unknown Origin

Table 30. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C/101°F on Several Occasions

Classical FUO	Nosocomial FUO	Neutropenic FUO	HIV-associated FUO
Duration >3 wk	Hospitalized patient Infection not present/incubating on admission	Neutrophil count <500/mL or is expected to fall to that level in 1-2 d	HIV infections Duration >4 wk for outpatients, >3 d for hospitalized patients
Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures

Causes of Nosocomial FUO
B, C, D, E

Bacterial and fungal infections of respiratory tract and surgical sites
Catheters (intravascular and urinary)
Drugs
Emboli

Etiology of Classic FUO

- infectious causes (~30%)
  - TB: extrapulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvic, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - other: viral (CMV, EBV, HIV), bacterial (brucellosis, bartonellosis), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin) and leukemias, multiple myeloma, myelodysplastic syndrome
  - solid tumours: renal cell carcinoma (most common), breast, liver (hepatocellular carcinoma), colon, pancreas, or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, polyarteritis nodosa), juvenile RA, Still disease
- miscellaneous (~20%)
  - drugs (e.g. antimicrobials, anti-arrhythmics), factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (e.g. familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
  - unknown in 30-50% despite detailed workup

Approach to Classic FUO

- careful and repeated history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - blood work: CBC and differential, electrolytes, urea, Cr, calcium profile, liver enzymes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, muscle enzymes, rheumatoid factor (RF), antinuclear antibody (ANA), serum protein electrophoresis (SPEP), blood film
  - cultures: blood (x3 sets), urine, sputum, stool C&S and O&P, other fluids as appropriate
  - serology: HIV, Monospot, CMV IgM, syphilis
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established

if no diagnosis with the above, consider empiric therapy vs. watchful waiting

  - without intervention: patients that remain undiagnosed despite extensive workup have good prognosis
- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent

Infections in the Immunocompromised Host

Factors that Compromise the Immune System

- general: age (very young or elderly), malnutrition
- immune disease: HIV, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

Table 31. Types of Immunodeficiency

Type	Conditions	Vulnerable To
Cell-Mediated Immunity	HIV, Hodgkin, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome	Latent viruses Fungi Parasites Non-tuberculosis *mycobacterium* (NTM)
Humoral Immunity	CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome	Encapsulated organisms (*S. pneumoniae, H. influenzae, N. meningitidis, Salmonella enterica* serotype *Typhi*, GBS)
Neutrophil Function	Chemotherapy, myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease	Catalase-producing organisms (*Staphylococcus, Serratia, Nocardia, Aspergillus*)

Febrile Neutropenia

Definition

- fever (≥38.3°C/101°F or ≥38.0°C/100.4°F for ≥1 h)
- neutropenia: ANC (absolute neutrophil count) <1.0
- ANC = WBC x (%neutrophils + %bands)
- severe neutropenia: ANC <0.5

Pathophysiology

- decreased neutrophil production
  - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - iatrogenic: cancer chemotherapy, radiation, drugs
  - deficiencies: vitamin B_{12}, folate
- increased peripheral neutrophil destruction
  - autoimmune: Felty's syndrome, SLE, antineutrophil antibodies
  - splenic sequestration

Epidemiology/Etiology

- most common life-threatening complication of cancer therapy
- 8 cases per 1000 cancer patients per yr in the U.S.
- causative organism identified only 1/3 of the time
- GN (especially *Pseudomonas*) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially *Candida, Aspergillus*)
- frequently associated with IV lines, mucosal or GI infection. Typhlitis (inflammation of cecum) is a rare complication, but can lead to serious infection and poor outcomes

Investigations
- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region for perianal abscess
- blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and nasopharyngeal swab for respiratory viruses, stool for testing if diarrhea
- CBC and differential, Cr, urea, electrolytes, AST/ALT, total bilirubin, chest imaging (CXR or CT)

Treatment
- most hospitals have their own specific protocol so check local guidelines first (see *Figure 16*)
- prophylaxis against febrile neutropenia (FN) with granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) decreases hospitalization without affecting mortality (indicated if risk of FN ≥20% or if FN has occurred in a previous chemotherapy cycle)

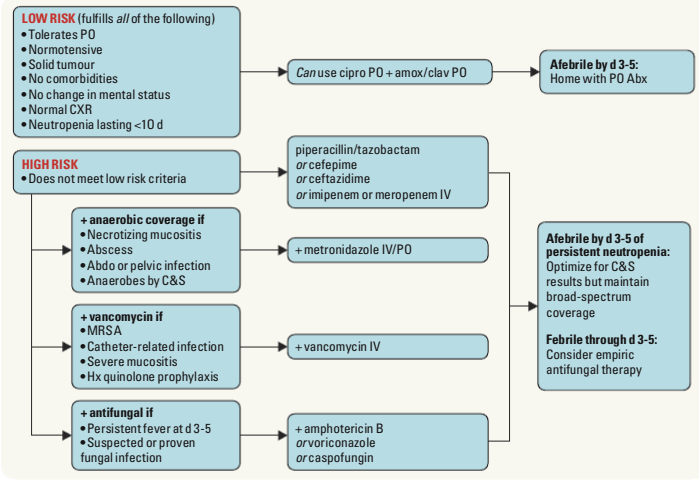


Figure 16. Example of treatment protocol for febrile neutropenia

Infections in Solid Organ Transplant Recipients

- infection is a leading cause of early morbidity/mortality in transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 mo post-transplant
  - donor-derived infections
  - bacterial infection of wound/lines/lungs, herpetic stomatitis
- common infections >1 mo post-transplant
  - viral (especially CMV, EBV, VZV)
  - fungal (especially *Aspergillus, Cryptococcus, P. jirovecii*)
  - protozoan (especially *Toxoplasma*)
  - unusual bacterial/mycobacterial infections (especially TB, *Nocardia, Listeria*)

Prophylactic Vaccinations Given Before Transplant
- to all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B, COVID-19
- in select patients: MMR, varicella, HPV, herpes zoster

Immune Reconstitution Inflammatory Syndrome

Definition
- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

Etiology
- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in patients with advanced HIV or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation

- can occur in response to multiple infections
  - Mycobacteria (*tuberculosis, avium complex*)
  - *Cryptococcus*
  - *Pneumocystis*
  - *Toxoplasma*
  - HBV and HCV
  - herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Molluscum contagiosum
  - COVID-19
- clinical features are dependent on the type and location of the pre-existing infection
- thought to be worse with quick increase in CD4 count and with lower pre-treatment CD4 count
- non-HIV conditions with documented immune reconstitution inflammatory syndrome (IRIS): solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

Epidemiology
- in HIV-positive patients starting ART, IRIS reported to affect ~10%

Investigations
- IRIS is a diagnosis of exclusion
- rule out drug reaction, medication non-adherence, drug resistance

Treatment
- continue ARV therapy in HIV-positive patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
- treat underlying infection; initiate treatment for some infections prior to ARV initiation
- consider starting corticosteroids/NSAIDs to decrease inflammatory response

A Simplified Look at Antibiotics

- general overview, see *Table 33, ID49* for more details

Table 32. Antibiotics Overview

Class and Drugs	GP							Anaerobes	GN					Atypicals	Other		
	Streptococcus spp.	*Staphylococcus* spp.			*Enterococcus* spp.		*C. difficile*		*H. influenzae*	*Neisseria* spp.		*Bacilli* (e.g. *E. coli, Klebsiella* spp.)	*Pseudomonas*	*Legionella, Chlamydia pneumoniae, Mycoplasma*	Rickettsia	*Chlamydia trachomatis*	*Syphilis*
		S. saprophyticus	MSSA	MRSA	*E. faecalis*	*E. faecium*				N. meningitidis	*N. gonorrhoeae*						
PENICILLINS																	
Penicillin G (IV)/ Penicillin V (PO)	✓							✓ Oral anaerobes except Gram(-) e.g. B. fragilis		✓							
Ampicillin (IV)/ Amoxicillin (PO)	✓				✓			✓ Oral anaerobes except Gram(-) e.g. B. fragilis									
Cloxacillin		✓	✓														
+β-LACTAM COMBINATION AGENTS																	
Amoxicillin-clavulanate	✓	✓	✓		✓			✓	✓			✓					
Piperacillin/ tazobactam	✓	✓	✓		✓			✓	✓	✓		✓	✓				
ceftolozane-tazobactam									✓			✓	✓				
Ceftrazidime-avibactam*									✓			✓	✓				
Meropenem-vaborbactam*									✓			✓	✓				
Imipenem-relebactam*									✓			✓	✓				
CEPHALOSPORINS (PO/IV)																	
1st generation: cephalexin/ cefazolin/cefadroxil	✓	✓	✓									✓					
2nd generation: cefuroxime/ cefprozil	✓	✓	✓						✓			✓					

Table 32. Antibiotics Overview

Class and Drugs	GP							Anaerobes	GN					Atypicals	Other		
	Streptococcus spp.	*Staphylococcus* spp.			*Enterococcus* spp.		*C. difficile*		*H. influenzae*	*Neisseria* spp.		*Bacilli* (e.g. *E. coli*, *Klebsiella* spp.)	*Pseudomonas*	*Legionella*, *Chlamydia pneumoniae*, *Mycoplasma*	Rickettsia	*Chlamydia trachomatis*	*Syphilis*
		S. saprophyticus	MSSA	MRSA	*E. faecalis*	*E. faecium*				N. meningitidis	*N. gonorrhoeae*						
3rd generation: cefixime/ cefotaxime, ceftriaxone	✓	✓	✓						✓	✓	✓	✓					
3rd generation: ceftazidime									✓			✓	✓				
4th generation: cefepime	✓	✓	✓						✓			✓	✓				
5th generation: ceftobiprole ceftaroline*	✓	✓	✓	✓					✓			✓					
Cefiderocol*									✓			✓	✓				
Aminoglycosides gentamicin tobramycin amikacin plazomicin*												✓	✓				
MACROLIDES																	
Erythromycin Clarithromycin									✓					✓			
Azithromycin									✓		✓			✓		✓	
FLUOROQUINOLONES																	
Ciprofloxacin										✓		✓	✓				
Levofloxacin	✓	✓	✓	✓	✓	✓			✓			✓	✓	✓			
Moxifloxacin	✓	✓	✓	✓	✓	✓		±	✓			✓	✓	✓			
Norfloxacin †spontaneous bacterial peritonitis (SBP) prophylaxis			✓		✓				✓		✓	✓	✓				
CARBAPENEMS																	
Imipenem	✓		✓		✓			✓	✓	✓	✓	✓	✓				
Meropenem	✓		✓					✓	✓	✓	✓	✓	✓				
Ertapenem								✓	✓	✓	✓	✓					
TETRACYCLINES																	
Doxycycline/ tetracycline/ minocycline	✓	✓	✓	✓	✓	✓			✓			✓		✓	✓	✓	✓
Tigecycline	✓		✓	✓	✓	✓		✓	✓			✓		✓	✓		
OTHERS																	
Vancomycin	✓		✓	✓	✓ (not VRE)	✓ (not VRE)	✓ (oral vancomycin for *C. difficile* gastroenteritis)										
Daptomycin	✓		✓	✓	✓	✓											
Linezolid	✓		✓	✓	✓	✓											
Metronidazole							✓	✓									
Clindamycin	✓		✓	✓				✓									
TMP/SMX			✓	✓								✓					
Nitrofurantoin		✓			✓	✓						✓					
Fosfomycin			✓	✓	✓	✓						✓					
Colistin									✓			✓	✓				

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Antimicrobials

Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S and clinical response
- if causative organism identified, use antibiotic to which organism is susceptible
- if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)

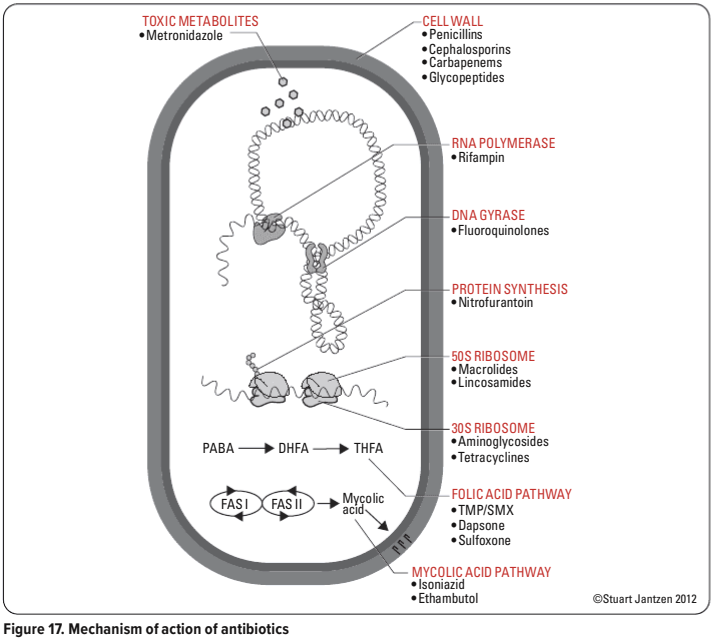

Figure 17. Mechanism of action of antibiotics

Reasons for Combination Therapy

- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. *Enterococcus* spp. causing endocarditis)
- To prevent emergence of resistance

Bactericidal Antibiotics	Bacteriostatic Antibiotics
"**V**ery **F**inely **P**roficient **A**t **CC**ell **M**ur**D**er"	"**ECSTaTiC**"
Vancomycin	**E**rythromycin (and other macrolides)
Fluoroquinolones	**C**lindamycin
Penicillin	**S**ulfamethoxazole
Aminoglycosides	**T**rimethoprim
Cephalosporins	**T**etracyclines
Carbapenems	**C**hloramphenicol
Metronidazole	
Daptomycin	

Table 33. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS					
Penicillins					
Benzyl penicillin - penicillin G IV/IM - penicillin V PO	GP except Staphylococcus, Enterococcus, N. meningitidis, Oral anaerobes Syphilis	Bactericidal: β-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan	Immediate allergy (IgE): anaphylaxis, urticaria Late-onset allergy (IgG): urticaria, rash, serum sickness Interstitial nephritis Dose related toxicity: seizures Diarrhea	Mild to moderately severe infections caused by susceptible organisms including: actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis	Hypersensitivity to penicillin
Aminopenicillin - ampicillin IV - amoxicillin PO (Amoxil®)	Same as penicillin AND *Enterococcus* *Listeria* Some strains of: *H. influenzae, E. coli, K. pneumoniae*	See above	See above	Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (AOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for *H. pylori* treatment, Lyme disease, pneumococcal pneumonia, UTI (amoxicillin and ampicillin) for most enterococci and susceptible GN pathogens	Hypersensitivity to penicillin or β-lactam antibiotics
Isoxazolyl penicillin - cloxacillin - methicillin - nafcillin - oxacillin	Methicillin-sensitive *Staphylococcus aureus*; streptococci	See above	See above	Bacterial infections caused by staphylococci and streptococci including skin and soft-tissue infections	Hypersensitivity to cloxacillin or any penicillin
β-lactam combinations - amoxicillin-clavulanate (Clavulin®, Augmentin®) - piperacillin/tazobactam (Tazocin®) -ceftolozane/tazobactam	Same as penicillin AND *Staphylococcus* *H. influenzae* *Enterococcus* Anaerobes (oral and gut) *P. aeruginosa* (piperacillin-tazobactam) Ceftolozane/tazobactam primarily used for resistant GN	β-lactamase produced by certain bacteria inactivate β-lactams Lactamase inhibitors prevent this process, preserving antibacterial effect of β-lactams	See above	Various β-lactamase producing bacteria, amoxicillin-clavulanate-sensitive bacteria including URTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections Ceftolozane-tazobactam, ceftazidime-avibactam, meroepenem-vaborbactam, and imipenem-relebacatam used to treat resistant GN infections	Hypersensitivity to penicillin or cephalosporin History of amoxicillin-clavulate-associated jaundice or hepatic dysfunction
Cephalosporins					
PO 1° cephalexin (Keflex®)	IV cefazolin (Ancef®)	GP Good with the exception of *Enterococcus* and MRSA	GN *E. coli, Klebsiella, Proteus, H. influenzae* (not all isolates)	Bactericidal: β-lactam inhibits PBP, prevents cross-linking of peptidoglycan, less susceptible to penicillinases	10% penicillin allergy cross-reactivity	Skin and soft tissue infections, prevention of surgical site infections (cefazolin); infections caused by susceptible organisms (especially *Staphylococcus* and *Streptococcus* infections)	Hypersensitivity to cephalosporins or other β-lactam antibiotics
2° cefuroxime (Ceftin®) cefprozil (Cefzil®)	cefuroxime (Zinacef®) cefoxitin	Weaker activity than 1°	More coverage than 1° (includes anaerobes)	See above	See above	Upper and lower RTI, pneumococcal pneumonia, soft tissue infections	See above
3° cefixime (Suprax®)	ceftriaxone (Rocephin®) cefotaxime (Claforan®) ceftazidime (Fortaz®)	*S. aureus* + streptococcal coverage (cefotaxime and ceftriaxone) especially *S. pneumoniae*	Broad coverage (includes *Pseudomonas* for ceftazidime only)	See above	~1% penicillin allergy cross-reactivity	Community-acquired pneumonia (cefotaxime, ceftriaxone), gonorrhea (ceftriaxone), community-acquired bacterial meningitis (ceftriaxone, cefotaxime), abdominal and pelvic infections (cefotaxime or ceftriaxone in combination with metronidazole), once-daily administration makes ceftriaxone convenient for outpatient IV therapy	Severe hypersensitivity (Type I) to other β-lactam antibiotics
4°	cefepime (Maxipime®)	Broad spectrum	Broad coverage including *Pseudomonas*	See above	See above	Empiric therapy for febrile neutropenia	See above
5°	Ceftobiprole (Zevtara ®) ceftaroline (Teflaro®)*	Broad coverage including MRSA	Broad coverage (except *Pseudomonas*)	See above	See above	Acute bacterial skin and skin structure infections, community-acquired pneumonia	See above
Other	Cefiderocol*	Broad spectrum	Broad coverage including Pseudomonas	See above	See above	Used to treat resistant GN infections	See above
Carbapenems							
imipenem (Primaxin®)	GP except MRSA GN including *Pseudomonas + Enterobacter*, extended-spectrum β-lactamases (ESBLs), anaerobes			β-lactam inhibits PBP and prevents cross-linking of peptidoglycan	Penicillin allergy cross-reactivity Seizures	Treatment of infections caused by GNB producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms	Hypersensitivity to imipenem Lowers seizure threshold
meropenem (Merrem®)	See above; does not cover *Enterococcus*			See above	See above	See above	Hypersensitivity to carbapenems
ertapenem (Invanz®)	GP except *Enterococcus*, MRSA GN including *Enterobacter* (but not *Pseudomonas*), anaerobes			See above	See above	See above; once-daily administration makes it convenient for outpatient IV therapy	Hypersensitivity to carbapenems

*Available in Canada through the Special Access Program

Table 33. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS					
Glycopeptides					
vancomycin (Vancocin®)	GP including MRSA, not VRE *C. difficile* if PO	Glycopeptide sterically inhibits cell wall synthesis	Red Man syndrome Nephrotoxicity Ototoxicity Thrombocytopenia	Severe or life-threatening GP infections, patients with β-lactam allergy May only be taken orally for severe *C. difficile* infection	Hypersensitivity to vancomycin
Other					
fosfomycin	GN (some coverage for *Pseudomonas* but lower compared to *Enterobacterales*) and GP (including *Enterococcus*)	Inhibiting cell wall synthesis at the initial step involving phosphoenolpyruvate synthase	PO – mild nausea, diarrhea possible IV – hypokalemia, hypernatremia, liver function test abnormalities	PO – uncomplicated urinary tract infections IV - complicated urinary tract infections, nosocomial lower RTI, osteomyelitis; bacterial meningitis	Hypersensitivity to fosfomycin
PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)					
Macrolides					
erythromycin (Erybid®, Eryc®) †This agent is rarely used due to GI upset	GP except *Enterococcus* GN: *Legionella, B. pertussis* "Atypicals": *Chlamydophila, Mycoplasma*	Binds to 50S ribosomal subunit inhibiting protein synthesis	GI upset Acute cholestatic hepatitis Prolonged QT	Susceptible RTI, pertussis, diphtheria, Legionnaires' disease, skin and soft tissue infections	Hypersensitivity to erythromycin Concurrent therapy with astemizole, terfenadine
clarithromycin (Biaxin®)	See above, some mycobacteria	See above	See above	Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for *H. pylori* treatment	Hypersensitivity to macrolides
azithromycin (Zithromax®)	See above, some mycobacteria	See above	See above	Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, *Campylobacter* infections if treatment indicated, chlamydia	Hypersensitivity to macrolides
Lincosamides					
clindamycin (Dalacin®)	GP except *Enterococcus*, most community-acquired MRSA anaerobes	Inhibits peptide bond formation at 50S ribosome	Pseudomembranous colitis and *C. difficile* GI upset	Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections	Hypersensitivity to clindamycin Infants <30 d Concurrent use or within 2 wk of monoamine oxidase (MAO) inhibitors
chloramphenicol	GP GN Anaerobes	Inhibits peptidyl transferase action of tRNA at 50S ribosome	Aplastic anemia Grey Baby syndrome	Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β-lactams	Hypersensitivity to chloramphenicol
linezolid (Zyvoxam®)	GP including VRE + MRSA	Binds 50S ribosome and prevents functional 70S initiation complex	HTN (acts as MAO inhibitor) Risks with prolonged use: myelosuppression, optic neuropathy, peripheral neuropathy	Vancomycin-resistant *Enterococcus faecium* infections including intra-abdominal, skin and skin structure, and urinary tract infections, MRSA infections as outpatient therapy	Hypersensitivity to linezolid, concurrent use or within 2 wk of MAO inhibitors
PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)					
Aminoglycosides					
gentamicin tobramycin amikacin (Amikin®) plazomicin*	GN (includes *Pseudomonas*)	Binds 30S subunit of ribosome inhibiting protein synthesis	Nephrotoxicity (reversible) Vestibular and ototoxicity (irreversible) Vestibular toxicity is the most important aminoglycoside toxicity	GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections	Pre-existing hearing loss and renal dysfunction
Tetracyclines					
tetracycline (Apo-Tetra®, Nu-TetraT®) minocycline (MinocinT®) doxycycline (Doxycin®) tigecycline (Tygacil®)	GP Anaerobes "Atypicals": *Chlamydophila, Mycoplasma, Rickettsia, Borrelia burgdorferi* *Treponema* Malaria prophylaxis (doxycycline) Tigecycline has activity against MRSA, VRE, and ESBL-producing *E. coli/K. pneumoniae*	Binds 30S subunit of ribosome inhibiting protein synthesis	GI upset Hepatotoxicity Fanconi's syndrome Photosensitivity Teratogenic Yellow teeth and stunted bone growth in children	*Rickettsial* infections, *Chlamydophila,* acne (tetracycline, minocycline), Pelvic Inflammatory Disease (PID) (step-down), malaria prophylaxis (doxycycline)	Severe renal or hepatic dysfunction Pregnancy or lactation Children under 12 yr

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Table 33. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
TOPOISOMERASE INHIBITORS					
Fluoroquinolones (FQs)					
ciprofloxacin (Cipro®) norfloxacin (Apo-Norflox®) ofloxacin (Floxin®) Respiratory FQs: levofloxacin (Levaquin®) moxifloxacin (Avelox®)	Variable GP activity GN (includes *Pseudomonas*) "Atypicals" levofloxacin and moxifloxacin cover *S. pneumoniae* moxifloxacin also has additional anaerobic coverage	Inhibits DNA gyrase	Headache, dizziness Allergy Seizures Prolonged QT Dysglycemia (levofloxacin, moxifloxacin) Tendonitis Tendon rupture	Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or management of "low-risk" febrile neutropenia (ciprofloxacin in combination with amoxicillin-clavulanate)	Pregnancy or lactation Children under 18 yr Concomitant use of medications that prolong QT interval
OTHER					
rifampin	GP cocci *N. meningitidis* *H. influenzae* Mycobacteria	Inhibits RNA polymerase	Hepatic dysfunction, P450 enzyme induction Orange tears/saliva/urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment for other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with *N. meningitidis* or HiB meningitis	Jaundice Not to be used as monotherapy (except for prophylaxis)
metronidazole (Flagyl®)	Anaerobes, protozoa	Forms toxic metabolites in bacterial cell which damage microbial DNA	Disulfiram-type reaction with EtOH Seizures Peripheral neuropathy	Protozoal infections (trichomoniasis, amebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections	Pregnancy with trichomoniasis Disulfiram within 2 wk, alcohol within 3 d Active neurological disorders Hypothyroidism Hypoadrenalism
daptomycin	GP, including MRSA and VRE	Binds to cell wall and forms channels leading to intracellular K depletion	Skeletal muscle injury at high doses (elevated creatine phosphokinase) Peripheral neuropathy	Bacteremia, endocarditis, skin and soft tissue, and other infections due to resistant GP infections including MRSA and VRE	Known hypersensitivity Inactivated by surfactant, therefore not used in MRSA pneumonia Tx
colistin	GN	Disrupts bacterial cell membranes	Renal toxicity	Bacteremia, pneumoniae	Hypersensitivity, renal failure
ANTI-METABOLITE					
trimethoprim-sulfamethoxazole (TMP/SMX) (Septra®, Bactrim®)	GP, especially *S. aureus* (including most MRSA) GN: enteric *Nocardia* Other: *Pneumocystis*, *Toxoplasma*	Inhibits folic acid pathway (TMP inhibits dihydrofolate reductase (DHFR) and SMX competes with (para-aminobenzoic acid) PABA)	Hepatitis Stevens-Johnson syndrome Bone marrow suppression Hyperkalemia Drug toxicity (increases free levels of many drugs, including glyburide, warfarin)	Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of *P. jirovecii* pneumonia	Hypersensitivity to TMP-SMX, sulfa drugs Infants <4 wk Hepatic or renal dysfunction Pregnancy and lactation
nitrofurantoin (MacroBID®, (Macrodantin®)	*Enterococcus*, *S. saprophyticus* GN (coliforms)	Reactive metabolites inhibit ribosomal protein synthesis	Cholestasis, hepatitis Hemolysis if G6PD deficiency Interstitial lung disease with chronic use	Lower UTI; not pyelonephritis or bacteremia	Anuria, oliguria, or significant renal impairment During or imminent labour Infants <1 mo of age
ANTI-MYCOBACTERIALS					
isoniazid (INH)	Mycobacteria	Inhibits mycolic acid synthesis	Hepatotoxicity Hepatitis Drug-induced SLE Peripheral neuropathy	Part of multidrug treatment for active TB, alone for treatment of latent TB	Drug-induced hepatitis or acute liver disease
rifampin (RIF)	Mycobacteria	Inhibits RNA polymerase	Hepatotoxicity P450 enzyme inducer Orange tears, saliva, urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment for other mycobacterial infections, adjunct for treating prosthetic device infection (bacterial biofilm), always use in combination with other antimicrobials to reduce emergence of resistance	Jaundice Not to be used as monotherapy (except for prophylaxis)
ethambutol	Mycobacteria	Inhibits mycolic acid synthesis	Loss of central and colour vision Neuropathy	Part of multidrug treatment for active TB and other mycobacterial infections	Renal failure
pyrazinamide (PZA)	Mycobacteria	Unknown	Hepatotoxicity Gout Gastric irritation	Part of multidrug treatment for active TB	Severe hepatic damage or acute liver disease Patients with acute gout
SULFONES					
dapsone sulfoxone	*M. leprae*, *P. jirovecii*, Toxoplasma	Inhibit folic acid synthesis by competition with PABA	Rash Drug fever Agranulocytosis	Part of multidrug treatment for *M. leprae*, part of treatment for *P. jirovecii* pneumonia (with TMP), *P. jirovecii* pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine	G6PD Deficiency

*Available in Canada through the Special Access Program

Table 34. Antibiotics for Selected Bacteria

Pseudomonas	*S. aureus*	*Enterococcus*	*H. influenzae*	Anaerobes
ciprofloxacin	cloxacillin (MSSA)	ampicillin	amoxicillin-clavulanate	metronidazole
gentamicin tobramycin amikacin	1º cephalosporin (MSSA)	amoxicillin	2º/3º cephalosporin	clindamycin
piperacillin/ tazobactam	clindamycin	vancomycin	macrolides (clarithromycin, azithromycin)	amoxicillin-clavulanate
ceftazidime	cotrimoxazole (including MRSA)	nitrofurantoin (lower UTI)	levofloxacin	cefoxitin
cefepime	vancomycin (including MRSA)	linezolid for VRE	moxifloxacin	piperacillin/tazobactam
imipenem	linezolid (including MRSA)	daptomycin for VRE		moxifloxacin
	daptomycin (including MRSA)	tigecycline for VRE		ertapenem, imipenem, meropenem
	tigecycline (including MRSA)	penicillin		
	doxycycline (MSSA/MRSA)	imipenem		

Antivirals

Table 35. Antivirals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ANTI-HERPESVIRUS				
acyclovir valacyclovir (Valtrex®) (prodrug of acyclovir)	HSV-1,2 VZV	Guanosine analogue inhibits viral DNA polymerase	PO: well-tolerated IV: nephrotoxicity, CNS	Hypersensitivity to acyclovir or valacyclovir
famciclovir (Famvir®) penciclovir	HSV-1,2 VZV	See above	Headache, nausea	Hypersensitivity to famciclovir or penciclovir
ganciclovir (Cytovene®) valganciclovir (prodrug of ganciclovir)	CMV HSV-1,2, VZV, HHV-6, EBV	See above	Hematologic: neutropenia, thrombocytopenia, anemia	Hypersensitivity to ganciclovir or valganciclovir Possible cross-hypersensitivity between acyclovir and valacyclovir
foscarnet	CMV Acyclovir-resistant HSV, VZV	Pyrophosphate analogue inhibits viral DNA polymerase	Nephrotoxicity Anemia Electrolyte disturbance	Hypersensitivity to foscarnet
OTHER ANTIVIRALS				
(pegylated) interferon-α-2a or-2b	Chronic hepatitis B	Inhibits viral protein synthesis	"Flu-like" syndrome Depression Bone marrow suppression	Hypersensitivity to any interferon Cannot use in combination with ribavirin if renal impairment
lamivudine (Epivir®)	Chronic hepatitis B, HIV	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*
tenofovir	Chronic hepatitis B, HIV	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*	See *HIV and AIDS, ID27*
entecavir	Chronic hepatitis B	Deoxyguanosine analogue Inhibits viral DNA polymerase reducing viral DNA synthesis	Increased serum ALT, bilirubin Skin rash Glycosuria, hyperglycemia GI Hematuria Fatigue, headache Increased serum Cr	Hypersensitivity to entecavir or any component of the formulation HIV co-infection (if monotherapy)
glecaprevir and pibrentasvir	Chronic hepatitis C	glecaprevir: HCV NS3/4A protease inhibitor pibrentasvir: HCV Nonstructural protein 5A inhibitor (NS5A) that is essential for viral RNA replication and virion assembly	Nausea, diarrhea Fatigue, headache Pruritus Increased serum bilirubin	Moderate/severe hepatic impairment or history of hepatic decompensation Coadministration: atazanavir, rifampin, atorvastatin, dabigatran, ethinyl estradiol, or simvastatin
sofosbuvir and velpatasvir	Chronic hepatitis C	velpatasvir: HCV NS5A protein inhibitor sofosbuvir: prodrug, inhibits NS5B RNA-dependent RNA polymerase	Fatigue, headache Increased serum creatine kinase Skin rash Increased serum lipase Nausea Insomnia, irritability Asthenia HBV reactivation (in HBV/HCV coinfection)	Hypersensitivity to sofosbuvir, velpatasvir, or any component of the formulation
ribavirin (Virazole®)	Chronic hepatitis C (in combination with direct-acting antivirals), RSV Lassa fever	Guanosine analog with multiple postulated mechanisms of action	Hemolytic anemia Rash, conjunctivitis Highly teratogenic	Pregnant women and partners Hemoglobinopathies Concomitant α interferon use
cidofovir	Adenovirus CMV retinitis Acyclovir and foscarnet resistant HSV	Deoxycytidine analogue Inhibits DNA synthesis	Nephrotoxicity (proximal tubule dysfunction)	Renal failure: probenecid can reduce renal toxicity

Table 35. Antivirals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
Neuraminidase inhibitors: zanamivir (Relenza®) oseltamivir (Tamiflu®)	Influenza A and B: treatment and prophylaxis	Inhibits neuraminidase, an enzyme required for release of virus from infected cells leading to prevention of viral aggregation	GI: nausea/vomiting, diarrhea Bronchospasm with zanamivir	Hypersensitivity to the neuraminidase inhibitors
remdesivir	Hospitalized COVID-19	Adenosine triphosphate analog Inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase Inhibits viral RNA synthesis	Bradycardia, hypotension Increased serum ALT, AST Hypersensitivity reactions (e.g. anaphylaxis, angioedema) Skin rash GI Prolonged prothrombin time Seizure	Hypersensitivity to remdesivir or any component of the formulation
nirmatrelvir/ritonavir (Paxlovid®)	COVID-19 infection within 5 days of symptom onset	nirmatrelvir: Peptidomimetic inhibitor of SARS-CoV-2 protease ritonavir: CYP3A inhibitor, increasing concentrations of nirmatrelvir	Hypertension Diarrhea, Dysgeusia Myalgia	Hypersensitivity to nirmatrelvir, ritonavir or any component of the formulation Co-administration of highly dependent CYP3A substrates or potent CYP3A inducers

Antifungals

Table 36. Antifungals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
POLYENES				
amphotericin B (liposomal formulation is less toxic)	Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis Pulmonary: Aspergillosis CNS: Cryptococcus	A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death	Nephrotoxicity Hypo/hyperkalemia Infusion reactions: chills, fevers, headache Peripheral phlebitis	Hypersensitivity to amphotericin or any component of the formulation
nystatin (oral, topical)	Candidiasis: mucocutaneous, GI, oral (thrush), vaginal	See above Not absorbed from the GI tract	GI: nausea/vomiting, diarrhea Highly toxic if given IV	Hypersensitivity to nystatin or any component of formulation
IMIDAZOLES				
clotrimazole (Canesten®)	Oral and vulvovaginal candidiasis Dermatomycoses	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Pruritus, skin irritation	Hypersensitivity to clotrimazole or any component of formulation
miconazole (Monistat®, Micozole®)	Vulvovaginal candidiasis Dermatomycoses		Vaginal burning Nausea/vomiting	Hypersensitivity to miconazole, milk protein concentrate, or any component of formulation
ketoconazole (Nizoral®)	Dermatomycoses Seborrheic dermatitis		Pruritus, skin irritation, GI nonspecific Results in decreased androgen and testosterone synthesis	Cross-sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant
TRIAZOLES				
fluconazole (Diflucan®)	*Candida* infections (mucosal and invasive) Cryptococcal meningitis (step-down therapy)	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Elevated liver enzymes GI nonspecific	Cross-sensitivity with other azoles unknown Terfenadine of multiple doses ≥400 mg CYP3A4 substrates (QTc prolongation risk)
itraconazole (Sporanox®)	Sporotrichosis Onychomycoses Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis		Elevated liver enzymes Rash GI Nonspecific HTN Hyperkalemia Peripheral edema	Cross-sensitivity with other azoles unknown Severe ventricular dysfunction Pregnant women or planning CYP2D6 inhibitors or eliglustat Hepatic and renal impairment
voriconazole (Vfend®)	Aspergillosis Candidiasis		Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma with long-term use in immunosuppressed patients Prolonged QT Periostitis Neurologic toxicity	Cross-sensitivity with other azoles unknown May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids, St. John's wort, venetoclax, ivabradine
posaconazole (Posanol®, Noxafil®)	Candidiasis Aspergillosis Mucormycosis		Elevated liver enzymes Headache Prolonged QT	Coadministration of cisapride, ergot alkaloids, or sirolimus CYP3A4 substrates: HMG-CoA reductase inhibitors (e.g. atorvastatin, lovastatin, simvastatin) QT interval prolonging (e.g. pimozide, quinidine)
isavuconazole	Candidiasis (esophageal) - off label for HIV patients Aspergillosis Mucormycosis		Peripheral edema Headache, fatigue, insomnia Hypokalemia GI Elevated liver enzymes Dyspnea, cough	Hypersensitivity to isavuconazole or any component of the formulation Strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) Strong CYP3A4 inducers (e.g. rifampin, carbamazepine, St. John's wort, long acting barbiturates) Moderate CYP3A4/5 inducers (e.g. efavirenz, etravirine) Familial short QT syndrome Pregnant women or planning

Table 36. Antifungals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ALLYLAMINES				
terbinafine (Lamisil®)	Dermatomycoses Onychomycoses	Inhibits enzyme needed for ergosterol synthesis	Rash, local irritation GI nonspecific Transaminitis	Active liver disease
ECHINOCANDINS				
caspofungin micafungin anidulafungin	Refractory aspergillosis Candidemia (azole-resistant)	Inhibits 1-3 β-D-glucan synthesis (needed for fungal cell wall)	Hepatotoxicity infusion and injection site reactions	

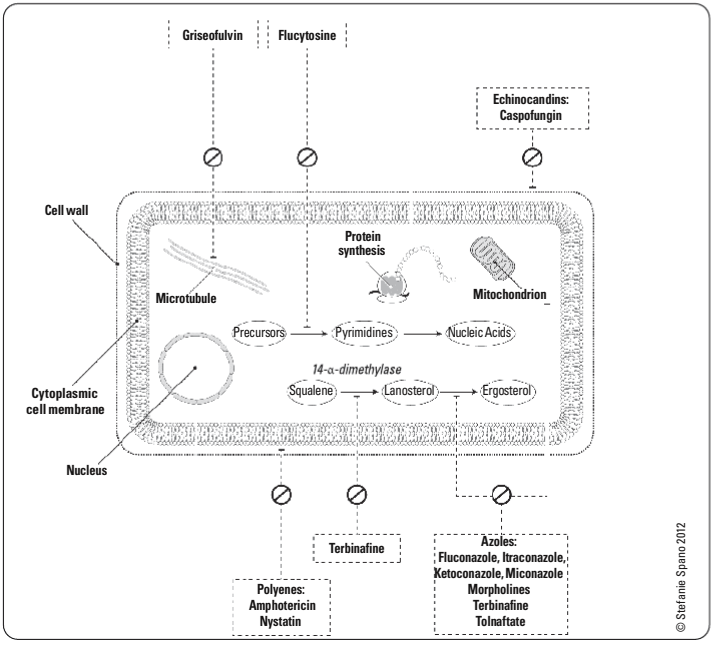

Figure 18. Mechanism of action of antifungals

Antiparasitics

Table 37. Antiparasitics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ANTIMALARIALS				
chloroquine	Malaria: treatment of erythrocytic phase of all five species of *Plasmodium* that infect humans Note: High resistance of *P. falciparum and P. vivax* in certain geographic areas	Inhibits parasite heme polymerase	CNS: blurred vision, retinopathy, dizziness Nonspecific GI (rare with prophylaxis)	Hypersensitivity to chloroquine or other 4-aminoquinoline Retinal or visual field changes
quinine	Malaria: treatment of all five species of *Plasmodium* that infect humans, including chloroquine-resistant *P. falciparum*		Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (nausea/vomiting, diarrhea), CNS (headache, fever) Hypoglycemia	Hypersensitivity to quinine, may have cross-sensitivity with quinidine Tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use Prolonged QT Myasthenia gravis
mefloquine (Lariam®)	Malaria: prophylaxis		CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, headache	History of seizures, psychosis, anxiety, depression, or other mental health diagnoses
primaquine	Malaria: treatment of liver hypnozoites of *P. vivax* and *P. ovale*; prophylaxis of all *Plasmodium* spp. *Pneumocystis jirovecii* (with clindamycin)	Interferes with mitochondrial function	Hemolytic anemia in G6PD deficient GI upset (take with food)	G6PD deficiency Concurrent or recent use of quinacrine Pregnancy
atovaquone/proguanil (Malarone®)	Malaria: treatment and prophylaxis of *P. falciparum*	Inhibits mitochondrial electron transport and dihydrofolate reductase	Nausea/vomiting, anorexia, diarrhea, abdominal pain (take with food)	Hypersensitivity to atovaquone or proguanil Severe renal impairment
artemisinin derivatives (artemether, artesunate, etc.) Note: marketed throughout the word in both endemic and non-endemic countries; neither licensed nor marketed in Canada, therefore available only via Health Canada Special Access Program	Malaria: treatment of all *Plasmodium* spp. Severe malaria (IV artesunate) Typically used in combination with a longer-acting agent from above	Binds iron, leading to formation of free radicals that damage parasite proteins	Transient neurologic deficits (nystagmus, balance disturbance) Transient neutropenia (at high doses of oral artesunate) Delayed hemolysis	Hypersensitivity to artemisinins
OTHER ANTI-PROTOZOAL				
iodoquinol (Diodoquin®)	Amebiasis: *E. histolytica, Dientamoeba fragilis, Balantidium coli, Blastocystis hominis*	Contact amebicide that acts in intestinal lumen by uncertain mechanism	GI: nausea/vomiting, diarrhea, abdominal pain CNS: headache, seizures, encephalitis	Hypersensitivity to any 8-hydroxyquinoline or iodine Patients with hepatic damage or optic neuropathy Pregnancy
metronidazole	Amebiasis: *E. histolytica*, *T. vaginalis, giardiasis, D. fragilis*	See *Antibiotics, ID50*		
nitazoxanide	*Cryptosporidium*, giardiasis, cyclosporiasis	Interferes with parasite anaerobic metabolism	Nausea/vomiting, diarrhea, abdominal pain, headache	Hypersensitivity to nitazoxanide
ANTI-HELMINTHICS				
praziquantel	*Schistosomiasis* and other flukes Tapeworms	Increases Ca^{2+} permeability of helminth cell membrane, causing paralysis and detachment	Nausea/vomiting, fever, dizziness	Ocular cysticercosis Concomitant use with strong CYP450 inducers
albendazole	Intestinal roundworms *Neurocysticercosis* *Echinococcus* Hydatid disease	Inhibits glucose uptake into susceptible parasites Microtubule inhibitor	Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis	Pregnancy Ocular cysticercosis or intraventricular cysticercosis
mebendazole (Vermox®)	Intestinal roundworms: pinworm, whipworm, hookworm, roundworm (e.g. *Ascaris*)	Inhibits microtubule formation and glucose uptake	Nonspecific GI	Pregnancy Infants
ivermectin	*Strongyloidiasis* *Onchocerciasis* Scabies	Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis	Nausea, bloating, diarrhea, myalgias, lightheadedness, headache	Hypersensitivity to ivermectin Pregnancy
diethylcarbamazine	Wuchereria bancrofti Loa loa	Thought to immobilize microfilariae and disrupt surface membrane to enhance killing by host immune system	Anorexia, nausea/vomiting, headache, drowsiness, encephalitis, retinal hemorrhage Mazzotti reaction if coinfected with onchocerciasis	Pregnancy Onchocerciasis High-grade microfilaremia due to *Loa loa*

Quick Reference: Common Infections and Their Antibiotic Management

- see Family Medicine, FM54

Landmark Infectious Diseases Trials

Trial Name	Reference	Clinical Trial Details
Respiratory Infections		
EPIC-HR	NEJM 2022;386:1397-1408	**Title:** Oral Nirmatrelvir for High-Risk, Non-hospitalized Adults with COVID-19 **Purpose:** To determine whether nirmatrelvir/ritonavir is safe and effective for the treatment of adults who are ill with COVID-19 and do not need to be in the hospital but are at an increased risk of developing severe illness. **Methods:** 2246 participants with confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive nirmatrelvir/ritonavir or placebo orally every 12 h for 5 d (10 doses total). **Results:** Primary outcome measure was proportion of participants with COVID-19 related hospitalization or death from any cause; incidence was lower on day 28 by 6.32% in nirmatelvir group compared to placebo (relative risk reduction of 89.1%; P<0.0001). **Conclusions:** In early treatment of patients with both symptomatic COVID-19 and at high risk of progressing to severe illness, nirmatrelvir/ritonavir significantly reduces hospitalization and death.
PINETREE	NEJM 2022;386:305-315	**Title**: Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients **Purpose**: To determine whether remdesivir in symptomatic, nonhospitalized patients with COVID-19 who are at high risk of disease progress prevents hospitalization. **Methods**: 562 patients were randomized within 7 d of symptoms onset to IV remdesivir (200 mg on day q1 and 100 mg on days 2 and 3) or placebo. Primary efficacy was a composite of COVID-19-reslated hospitalization or death from any cause by day 28. **Results**: COVID-19-related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group. **Conclusions**: Among non-hospitalized patients who were at high risk for COVID-19 progression, a 3-day course of remdesivir resulted in an 87% lower risk of hospitalization or death than placebo.
ACTT-1	NEJM 2020;383:1813-26	**Title**: Remdesivir for the Treatment of Covid-19 — Final Report **Purpose**: To determine if remdesivir is effective against patients hospitalized with COVID-19 lower respiratory tract infection **Methods**: 1062 patients were randomized to either remdesivir (200 mg loading dose on day 1, followed by q100 mg daily for up to 9 additional days) or placebo for up to 10 d. Primary outcome: time to recovery define as either discharge from hospital or hospitalization for infection control purposes only. **Results**: Mean time to recovery for those randomized to remdesivir was 10 d compared to 15 d among those with placebo. Kaplan-Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15. **Conclusions**: Remdesivir was superior to placebo in shortening time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection.
RECOVERY	NEJM 2021;384:693-704	**Title:** Dexamethasone in Hospitalized Patients with COVID-19 **Purpose:** To assess if glucocorticoids can protect against inflammation-mediated lung injury and reduce progression to respiratory failure and death. **Methods:** 6425 hospitalized SARS-CoV-2 patients were randomized to receive either (1) dexamethasone (oral or IV, 6 mg daily) for up to 10 d or (2) usual standard of care alone. **Results:** Dexamethasone significantly reduced incidence of death as compared to usual care alone in patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; RR 0.64; 95% CI 0.51-0.81) and among those receiving oxygen (23.3% vs. 26.2%; RR 0.82; 95% CI 0.72-0.94) but not among those without respiratory support (17.8% vs. 14.0%; RR 1.19; 95% CI 0.92-1.55). **Conclusion:** In patients hospitalized with COVID-19, dexamethasone lowers 28-d mortality in those receiving invasive mechanical ventilation or oxygen alone.
PneumA	JAMA 2003;290:2588-98	**Title:** Comparison of 8 vs. 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults: A Randomized Trial **Purpose:** To identify the optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP). **Methods:** 401 patients with VAP diagnosed by quantitative culture of bronchoscopic specimens who had received initial empiric antibiotic therapy were randomly assigned to receive either 8 d or 15 d of antibiotic therapy (regimen selected by treating physician). **Results:** As compared to 15-d therapy, 8-d therapy did not result in a significant difference in mortality (18.8% vs. 17.2% in 8-d and 15-d group, respectively; difference, 1.6%; 90% CI, -3.7% to 6.9%) or recurrent infections (28.9% vs. 26.0%; difference, 2.9%; 90% CI, -3.2% to 9.1%). 8-d therapy was associated with more mean antibiotic-free days (13.1 vs. 8.7; P<0.001). **Conclusion:** 8- and 15-d antibiotic treatment regimens demonstrated comparable clinical efficacy against VAP among patients who had received appropriate initial empiric therapy.
Meningitis		
Dexamethasone in Adults with Bacterial Meningitis. Gans et al. 2002	NEJM 2002;347:1549-56	**Title:** Dexamethasone in Adults with Bacterial Meningitis **Purpose:** To assess the efficacy of corticosteroids as an adjuvant treatment of acute bacterial meningitis in adults. **Methods:** 301 patients were randomly assigned to receive dexamethasone (10 mg) or placebo 15-20 min before or with the first dose of antibiotics and subsequently every 6 h for 4 d. **Results:** Dexamethasone treatment was associated with a significant reduction in the risk of an unfavourable outcome, defined as a score of 1-4 on the Glasgow Outcome Scale at 8 wk (relative risk (RR), 0.59; 95% CI, 0.37-0.94; P=0.03), as well as a significant reduction in in mortality (RR, 0.48, 95% CI, 0.24-0.96; P=0.04). **Conclusion:** In adults with acute bacterial meningitis, early treatment with dexamethasone significantly improves outcomes and does not increase the risk of GI bleeding.
Infective Endocarditis		
POET	NEJM 2019;380:415-24	**Title:** Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis **Purpose:** To investigate whether a change from IV to oral antibiotics in stable left-sided IE would result in efficacy and safety profiles similar to those with continued IV treatment. **Methods:** 400 adults with IE on the left side of the heart, in stable condition, being treated with IV antibiotics (minimum 10 d) were randomized to continue IV treatment or to switch to oral antibiotics. Primary Outcome: Composite of all-cause mortality, embolic events, unplanned cardiac surgery, or relapse of bacteremia with the primary pathogen, from the time of randomization until 6 mo following completion of antibiotics. **Results:** The primary composite outcome occurred in 12.1% in the IV group and 9.0% in the oral group (between-group difference, 3.1 percentage points; 95% CI, -3.4 to 9.6; P=0.40), thus meeting noninferiority. **Conclusion:** Shifting to oral antibiotics was noninferior to continued IV antibiotics in patients with IE on the left side of the heart in stable condition.

Trial Name	Reference	Clinical Trial Details
Intraabdominal Infections		
STOP-IT	NEJM 2015;372:1996-2005	**Title:** Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection **Purpose:** To determine the appropriate duration of antimicrobial therapy for intraabdominal infection. **Methods:** 518 patients with complicated intraabdominal infection and adequate source control were randomly assigned to receive a fixed course of antibiotics for 4±1 d (experimental group) or until 2 d following the resolution of fever, leukocytosis, and ileus, up to maximum 10 d (control group). **Results:** There were no significant differences in the rates of surgical-site infection, recurrent intraabdominal infection, or death between treatment groups (21.8% vs. 22.3% in the experimental and control groups, respectively; absolute difference, -0.5; 95% CI, -7.0 to 8.0; P=0.92). The experimental group experienced a significantly shorter median duration of antibiotic therapy (4.0 d vs. 8.0 d; absolute difference, -4.0; 95% CI, -4.7 to -3.3; P<0.001). **Conclusion:** The outcomes after fixed-duration antibiotic therapy were similar to those after a longer course of antibiotics in patients with intraabdominal infections with adequate source control.
HIV and AIDS		
iPrEx	NEJM 2010;363:2587-99	**Title:** Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex With Men **Purpose:** To investigate the efficacy and safety of antiretroviral chemoprophylaxis for the prevention of HIV acquisition. **Methods:** 2499 HIV-seronegative men or transgender women who have sex with men were randomly assigned to receive emtricitabine plus tenofovir disoproxil fumarate (FTC-TDF), or placebo daily. **Results:** During median 1.2 yr follow-up, 100 participants became infected (36 in the FTC-TDF group vs. 64 in the placebo group), representing a 44% reduction in the incidence of HIV (95% CI, 15-63; P=0.005). Similar rates of serious adverse events were observed in both groups (P=0.57). **Conclusion:** Preexposure prophylaxis with antiretrovirals significantly reduced HIV infection risk in HIV-negative men and transgender women who have sex with men.
Prevention of HIV-1 Infection With Early Antiretroviral Therapy. Cohen et al. 2011	NEJM 2011;365:493-505	**Title:** Prevention of HIV-1 Infection With Early Antiretroviral Therapy **Purpose:** To investigate if immediate antiretroviral therapy could limit the transmission of HIV in serodiscordant couples. **Methods:** 1763 HIV-1-positive adults with an HIV-negative partner were randomly assigned to receive antiretroviral therapy either immediately or after a decline in the CD4 count or the onset of HIV-1-related symptoms. **Results:** Of the 39 HIV-1 transmissions observed, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6-1.3). Of the 28 linked transmissions, 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01-0.27; P<0.001). **Conclusion:** Rates of HIV-1 transmission and clinical events were reduced by early initiation of antiretroviral therapy, suggesting personal and public health benefits.
Sepsis and Septic Shock		
CORTICUS	NEJM 2008;358:111-24	**Title:** Hydrocortisone Therapy for Patients With Septic Shock **Purpose:** To investigate the efficacy of hydrocortisone administration in patients with septic shock who were either responsive or unresponsive to corticotropin. **Methods:** 499 patients were randomly assigned to receive 50 mg IV hydrocortisone or placebo every 6 h for 5 d with dose tapering over the following 6 d. **Results:** No significant difference in mortality at 28 d between patients in groups that did not respond to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, P=0.69) or between those that did response to corticotropin (28.8% and 28.7%, P=1.00). **Conclusion:** Survival was not improved by hydrocortisone in patients with septic shock.
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. Brunkhorst et al. 2008	NEJM 2008;358:125-39	**Title:** Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis **Purpose:** To investigate the role of intensive insulin therapy and the choice of either crystalloids or colloids in patients with severe sepsis. **Methods:** Patients received either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch or modified Ringer's lactate for fluid resuscitation. **Results:** Trial stopped for safety reasons. Intensive insulin therapy was associated with increased rates of hypoglycemia (17.0% vs. 4.1%, P<0.001) and serious adverse events (10.9% vs. 5.2%, P=0.01). Higher rates of acute renal failure and renal-replacement were seen in pentastarch as compared to Ringer's lactate. **Conclusion:** In critically ill patients with sepsis, intensive insulin therapy increased the risk of serious adverse events related to hypoglycemia. Pentastarch was harmful.
Bone and Joint Infections		
OVIVA	NEJM 2019;380:425-36	**Title:** Oral versus Intravenous Antibiotics for Bone and Joint Infection **Purpose:** To assess if oral antibiotics are noninferior to IV antibiotic treatment for managing complex orthopaedic infections. **Methods:** Within 1 wk post-surgery, 1054 patients were randomly assigned to receive IV or oral antibiotics for 6 wk. Both groups were permitted follow-on oral antibiotics. **Results:** There was no significant difference in risk of treatment failure between oral and IV groups (-1.4%; 95% CI, -5.6-2.9), indicating noninferiority. There was no significant difference in the rates of serious adverse events between groups. **Conclusion:** Oral antibiotics were noninferior to IV antibiotics for the treatment of complex orthopaedic infections when used for 6 wk.
DATIPO	NEJM 2021;384:1991-2001	**Title:** Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection **Purpose:** To identify the appropriate duration of antimicrobial therapy for the management of prosthetic joint infection. **Methods:** 410 patients with microbiologically confirmed prosthetic joint infection that had been managed with an appropriate surgical procedure were randomly assigned to receive either 6 wk or 12 wk of antibiotic therapy as soon as possible after surgery. **Results:** Rates of persistent infection were significantly higher in the 6-wk group as compared to the 12 wk group (18.1% vs. 9.4%; risk difference, 8.7%; 95% CI, 1.8%-15.6%). **Conclusion:** Antibiotic therapy for 6 wk was not noninferior to 12-wk therapy and resulted in more unfavourable outcomes in patients with prosthetic joint infections managed with standard surgical procedures.

Trial Name	Reference	Clinical Trial Details
Blood and Tissue Infections		
Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. Zongo et al. 2021	NEJM 2021; 385:1005-1017	**Title:** Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention **Purpose:** The study compared the efficacy of RTS,S to that of SMC, which is the standard treatment for children in areas with highly seasonal malaria transmission. **Methods**: Randomly assigned 6861 children 5 to 17 mo of age to receive sulfadoxine-pyrimethamine and amodiaquine (2287 children [chemoprevention-alone group]), RTS,S/AS01E (2288 children [vaccine-alone group]), or chemoprevention and RTS,S/AS01E (2286 children [combination group]) **Results:** Demonstrated that not only is RTS,S comparable to SMC in preventing malaria, but that combining the two interventions is markedly superior to either intervention alone. **Conclusion:** Use of the two interventions together resulted in an approximately 70 percent further reduction in malaria deaths and hospitalizations, and a 60 percent reduction in uncomplicated malaria over use of SMC alone.
BENEFIT	NEJM 2015;373:1295-306	**Title:** Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy **Purpose:** To investigate the efficacy of trypanocidal therapy in patients with Chagas' cardiomyopathy. **Methods:** 2854 patients with Chagas' cardiomyopathy were randomly assigned to receive benznidazole or placebo for up to 80 d. **Results:** Rates of conversion to negative *Trypanosoma cruzi* PCR results were 66.2% in the benznidazole group and 33.5% in the placebo group at the end of treatment, 55.4% and 35.3% at 2 yr, and 46.7% and 33.1% at >5 yr (P<0.001 for all). PCR conversion rates did not correspond to clinical outcomes. **Conclusion:** In patients with Chagas' cardiomyopathy, trypanocidal therapy reduced serum parasite levels but did not improve cardiac deterioration.
Fungal Infections		
Voriconazole Versus Amphotericin B for Primary Therapy of Invasive Aspergillosis. Herbrecht et al. 2002	NEJM 2002;347:408-15	**Title:** Voriconazole Versus Amphotericin B for Primary Therapy of Invasive Aspergillosis **Purpose:** To compare voriconazole vs. amphotericin B for primary therapy of invasive aspergillosis. **Methods:** 277 patients randomly assigned to receive IV voriconazole followed by oral voriconazole BID or IV amphotericin B deoxycholate. **Results:** Successful outcomes occurred in 52.8% of patients on voriconazole and 31.6% on amphotericin B at wk 12 (absolute difference, 21.2%; 95% CI, 10.4-32.9). Rate of survival was 70.8% in the voriconazole group and 57.9% in the amphotericin B group (hazard ratio, 0.59; 95% CI, 0.40-0.88). Voriconazole was associated with significantly fewer severe adverse events. **Conclusion:** Initial therapy with voriconazole is more clinically effective with fewer side effects than the standard approach with amphotericin B.

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Acronyms

CF	cystic fibrosis	GA	gestational age	MCADD	medium chain acyl-CoA dehydrogenase deficiency	NGS	next generation sequencing
CNV	copy number variant	GS	genome sequencing	MLPA	multiplex ligation-dependent probe assay	PKU	phenylketonuria
(W)ES	(whole) exome sequencing	GSD	glycogen storage disease	MSUD	maple syrup urine disease	SNP	single nucleotide polymorphism
(W)GS	(whole) genome sequencing	LCHAD	long chain 3-hydroxyacyl-CoA dehydrogenase deficiency			VLCAD	very long chain acyl-CoA dehydrogenase deficiency
FISH	fluorescence in situ hybridization						

Introduction to Genetics

Common Terms

- **penetrance**: probability that a gene variant is observably expressed in an individual who carries it
- **expressivity**: extent of gene expression – refers to the range of variation seen in a phenotype for a certain genotype
- **genetic heterogeneity**: when a phenotype/genetic disorder can be caused by different genotypes, due to genetic variation within the same gene (allelic heterogeneity) or in different genes (locus heterogeneity)
- **phenotypic heterogeneity**: pathogenic variants in the same gene result in multiple clinical manifestations and varying degrees of severity
- **mosaicism**: presence of two or more genotypes (e.g. chromosome patterns or gene variants) in the cells of the same person
- **nondisjunction**: a cell division error in which chromosomes fail to segregate, resulting in daughter cells with fewer or more chromosomes than expected
- **uniparental disomy**: inheritance of two full or partial copies of a chromosome from one parent and no corresponding full/partial chromosome from the other parent
- **allele**: an abnormal number of chromosomes in the cell due to loss or duplication

Genetic Variation

- a variant is a permanent change in the nucleotide sequence that differs from the most common nucleotide sequence (reference sequence)
- variants are classified based on their likelihood of disrupting the function of the gene product. The American College of Medical Genetics and Genomics has created a commonly used method for classifying variants for single gene disorders:
  - benign: not associated with genetic disease
  - likely benign: probably not associated with genetic disease, but insufficient evidence to classify as benign
  - variant of uncertain significance (VUS): insufficient evidence to classify variant as benign or pathogenic
  - likely pathogenic: 90% likely to be pathogenic, and clinically treated as a pathogenic variant
  - pathogenic: known to be associated with genetic disease
- nomenclature no longer used in clinical genetics:
  - mutation: previously synonymous with pathogenic variant. Now this term is only used to describe the actual process of genetic change
  - polymorphism: a variant that is relatively common in the population and not typically associated with a genetic disease. This term is used only in the context of population genetics

Types of Genetic Variation

- deletions or duplications of a whole gene(s) caused by aneuploidy, unbalanced chromosome rearrangements, or copy number variants (e.g. 22q11.2 deletion or DiGeorge syndrome; 17p11.2 duplication or Potocki-Lupski syndrome)
- disruption of a gene: inversions, balanced chromosome rearrangements
- variants that cause alteration in the protein coding sequence: missense (encodes for a different amino acid), nonsense (encodes for a premature stop codon), frameshift (deletion/insertion of a number of nucleotides that is not a multiple of 3, thus shifting the reading frame)
- variants that affect the transcription of a gene
- variants that affect splicing

Single Gene Disorders

- traits or disorders determined by variation occurring in a specific gene, which often follow a Mendelian inheritance pattern
- autosomal inheritance: disorder is caused by pathogenic variants in a gene located on chromosomes 1-22 (the autosomes)
  - autosomal dominant: one copy of a gene with a pathogenic variant is sufficient to cause a trait/disorder
  - autosomal recessive: both copies of a gene must have pathogenic variants to cause a trait/disorder; an individual with one copy of a pathogenic gene variant is a carrier
- sex-linked inheritance: when disease is caused by pathogenic variants in a gene on the X or the Y chromosome. Because the X chromosome contains more genes than the Y chromosome, almost all sex-linked traits are X-linked. X-linked inheritance generally results in a trait/disorder that is seen more commonly or with greater severity in males than females
  - e.g. Hemophilia A, Duchenne muscular dystrophy

Triplet Repeat Expansions

- disorders where the number of trinucleotide repeats in certain genes exceeds the normal number and results in altered gene expression or production of an abnormal protein
  - these disorders can demonstrate genetic anticipation, where signs and symptoms are more severe and appear at an earlier age from one generation to the next due to expansion of the triplet repeat number
  - length of expansion segment is often proportional to severity of clinical phenotype
- e.g. Fragile X syndrome, Huntington disease

Imprinting Disorders

- imprinted genes are expressed entirely from either the maternal or paternal allele, depending on the gene (parent-of-origin gene expression)
- imprinting is determined by allele-specific epigenetic mechanisms (i.e. modifications to DNA other than a change in the underlying sequence, such as DNA methylation and/or histone modifications)
- disorders occur when a pathogenic variant disrupts the normally expressed allele of an imprinted gene or through uniparental disomy of the normally silenced allele
- e.g. Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome

Mitochondrial Disorders

- disorders caused by pathogenic variants in mitochondrial DNA or in nuclear genes whose protein products are important for mitochondrial function
- high phenotypic heterogeneity
- mitochondrial disorders caused by pathogenic variants in nuclear genes demonstrate Mendelian inheritance (e.g. Alpers syndrome caused by autosomal recessive pathogenic variants in *POLG*)
- disorders caused by pathogenic variants in mitochondrial DNA are maternally inherited by all offspring as all mitochondria and associated mitochondrial DNA in the embryo comes from the maternal ovum, with no paternal contribution of mitochondria
- e.g. mitochondrial encephalomyopathy and lactic acidosis with stroke-like episodes syndrome (MELAS)

Common Indications for Genetic Referrals

- preconception and prenatal: abnormal prenatal screening test, fetal anomaly, recurrent pregnancy loss, personal or family history of a genetic condition, positive carrier screening test, consanguinity
- pediatric: major and/or multiple minor congenital anomalies, developmental delay, abnormal newborn screen, unusual growth pattern, abnormal pubertal development, connective tissue disorders, congenital hypo- or hypertonia
- adult: family history of adult-onset genetic condition (e.g. Huntington disease), personal or family history of cancer concerning for genetic cause, bleeding or clotting disorder, early onset vision or hearing loss, intellectual disability, leukodystrophies, muscular dystrophy, movement disorders (e.g. ataxia, dystonia, chorea), and metabolic diseases

Pedigrees

- diagrams of a family tree that show the pattern/distribution of phenotypes for a genetic disorder within that family, often across multiple generations
- pedigrees generally indicate sex assigned at birth, with or without genetic confirmation of sex chromosomes; when counselling gender diverse patients (including transgender and non-binary patients), physicians should affirm the patient's gender identity, while clarifying the role of sex assigned at birth or chromosomal sex in determining genetic features for the pedigree

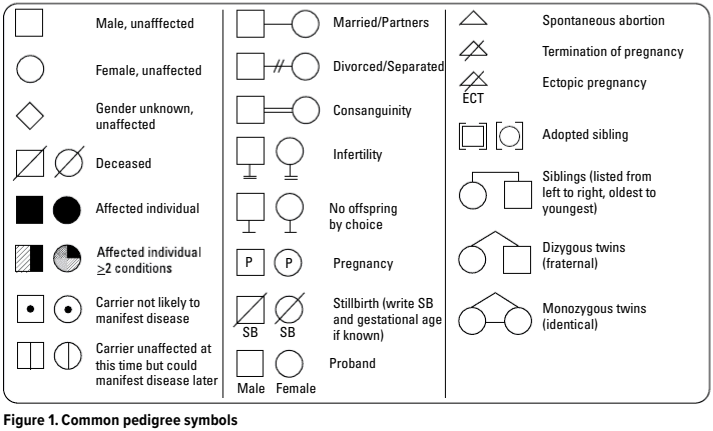

Figure 1. Common pedigree symbols

Meta-analysis of the Diagnostic and Clinical Utility of Genome and Exome Sequencing and Chromosomal Microarray in Children
Genomic Med 2018;3:16
Purpose: To compare the diagnostic and clinical utility of WGS and WES to that of chromosomal microarray.
Methods: A systematic review and meta-analysis of the literature.
Results: 37 studies were included (20068 children). Diagnostic utility of WGS (0.41, 95% CI 0.34-0.48) and WES (0.36, 95% CI 0.33-0.40) were greater than chromosomal microarray (0.10, 95% CI 0.08-0.12). The clinical utility of WGS (0.27, 95% CI 0.17-0.40) and WES (0.17, 95% CI 0.12-0.24) were higher than chromosomal microarray (0.06, 95% CI 0.05-0.07) and this difference was significant for WGS vs. chromosomal microarray (P<0.0001).
Conclusion: The diagnostic and clinical utility of WGS and WES is greater than that of chromosomal microarray.

Genetic Testing and Counselling

Common Terms

- presymptomatic genetic testing: used to determine whether individuals without current symptoms, but with a known family history of a genetic disease, carry the familial pathogenic variant associated with the disease
- newborn screening: performed within the first few days of life to detect treatable and potentially fatal disorders before symptoms arise to allow for early therapy
- preconception genetic counselling: pre-pregnancy evaluation to assess the risk of having a child with an inherited condition
- preimplantation genetic diagnosis: genetic testing of in vitro fertilized embryos for specific genetic conditions before uterine transfer

Table 1. Common Genetic Tests

Test	Karyotype	FISH	Microarray Analysis	Sanger Sequencing	NGS	MLPA	Repeat-Primed PCR
Technique	Microscopic analysis of chromosomes with a nucleic acid stain that shows large changes in the number or structure of chromosomes; can detect large CNVs	A fluorescent-tagged DNA probe used to identify a gain, loss, or rearrangement of chromosomal material or specific DNA sequence	A collection of DNA probes attached to a solid surface to which test DNA hybridize in order to determine copy number of DNA regions	A method of DNA sequencing which is based on the selective incorporation of chain-terminating nucleotides during replication	High-throughput method used to sequence multiple genes in parallel; NGS is the technology used for panel sequencing, (W)ES, and (W)GS	High-throughput multiplex PCR assay, which uses probes to evaluate the relative copy number of each DNA sequence	PCR amplification method which uses paired primers to generate different sized amplicons, due to multiple annealing sites on the template
Uses/Indications	Useful in identification of major aneuploidies, structural chromosomal rearrangements, chromosomal changes related to hematological conditions, or other genetic diseases related to chromosome structure	Can confirm the presence or absence of specific DNA sequences and localize them. It has good resolution for microdeletions and small translocations May be used to detect aneuploidies, perform gene mapping, identify oncogenes, and identify circulating tumour cells	Microarray analysis can identify small deletions or duplications of genetic material anywhere in the genome. Commonly indicated when there is developmental delay/ autism or two or more congenital anomalies	The "gold-standard" method for identification of single nucleotide variants in the gene(s) known to cause a suspected syndrome	Limited indications (vary by province) but may include: limit further invasive diagnostics and facilitate early intervention when there is multisystem involvement, or when the differential diagnosis includes ≥2 conditions that would require separate genetic tests	Can detect small copy number variants, at an exon-level resolution Widely used due to low cost, simplicity, and broad availability of commercially developed assays	Used to determine the number of repeats. Used in diagnostic or predictive testing in symptomatic or at-risk individuals

- see Obstetrics, OB7 for information on prenatal screening tests

Differences in Morphology

Congenital Anomalies

Minor and Major Anomalies

- minor anomaly: physical difference that is of no significant medical or cosmetic consequence to the patient (e.g. ear pit/tag, single palmar crease)
- major anomaly: physical difference that creates significant medical, surgical, or cosmetic problems for the patient (e.g. ventricular septal defect, cleft lip)

Mechanisms for Anomalies

- malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
- disruption: results from the extrinsic breakdown of, or interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
- deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter deformation sequence)
- dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g. skeletal dysplasia)

Multiple Anomalies

- association: non-random occurrence of multiple independent anomalies that appear together more often than would be predicted by chance, but are not known to have a single underlying etiology (e.g. VACTERL association)
- sequence: related anomalies that originate from a single initial major anomaly or precipitating factor that changes the development of other surrounding or related tissues or structures (e.g. Potter sequence or Pierre-Robin sequence)
- syndrome: a pattern of anomalies that occur together and are known or thought to have a single cause (e.g. CHARGE syndrome)

VACTERL Association
Vertebral dysgenesis
Anal atresia (imperforate anus) ± fistula
Cardiac anomalies
Tracheo**E**sophageal fistula ± esophageal atresia
Renal anomalies
Limb anomalies

Approach to the Patient with Physical Differences

Check the umbilical cord for 2 arteries and 1 vein. The presence of a single umbilical artery may be associated with other congenital anomalies

General Approach

- are the anomalies major or minor?
- what is the mechanism underlying the anomaly?
- do the anomalies fit as part of an association, sequence, or syndrome?
- are the anomalies seen in other family members?

History

- prenatal/obstetrical history (see Obstetrics, OB4) with particular attention to potential teratogenic exposures, developmental history (see Pediatrics, P26), and past medical history
- complete three generation family pedigree: health history, consanguinity, multiple miscarriages/stillbirths, neonatal deaths, congenital defects, developmental delay/autism, ethnicity

Physical Exam

- compare features with other family members

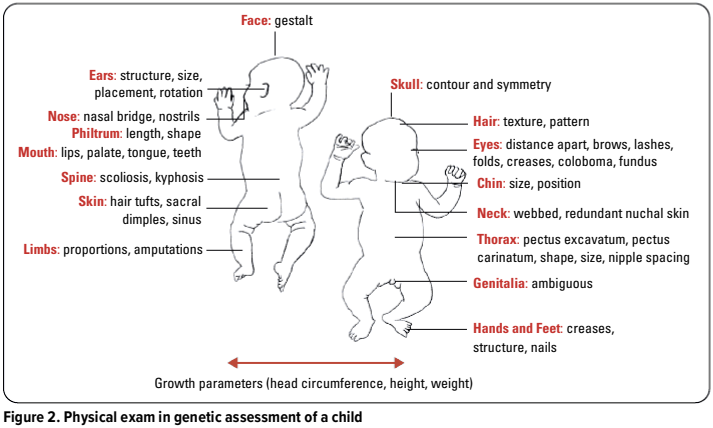
Face: gestalt
Ears: structure, size, placement, rotation
Nose: nasal bridge, nostrils
Philtrum: length, shape
Mouth: lips, palate, tongue, teeth
Spine: scoliosis, kyphosis
Skin: hair tufts, sacral dimples, sinus
Limbs: proportions, amputations
Skull: contour and symmetry
Hair: texture, pattern
Eyes: distance apart, brows, lashes, folds, creases, coloboma, fundus
Chin: size, position
Neck: webbed, redundant nuchal skin
Thorax: pectus excavatum, pectus carinatum, shape, size, nipple spacing
Genitalia: ambiguous
Hands and Feet: creases, structure, nails
Growth parameters (head circumference, height, weight)

Figure 2. Physical exam in genetic assessment of a child

Investigations

- screening for TORCH infections (toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, herpes infection)
- serial photographs
- x-rays for bony abnormalities
- abdominal U/S and echocardiography to rule out structural abnormalities of organs
- brain imaging, especially if neurodevelopmental/neurological findings
- cytogenetic studies
  - chromosomal microarray analysis (SNP array) if developmental delay/autism or two or more congenital anomalies
  - FISH if aneuploidy syndrome (e.g. trisomy 13, 18, or 21) suspected
  - consider karyotype if a known aneuploidy syndrome is recognized or if there is a family history of a chromosomal rearrangement such as a translocation
- biochemistry: various biochemical tests, specific enzyme assays (e.g. for lysosomal storage diseases)
- single gene testing, gene panel testing, ES, GS
- sensory evaluations including audiology, ophthalmology or optometry

Management

- recurrence risk and prenatal counselling
- referral for specialized medical care or genetic care for symptomatic management
- patient education, connect to social and psychological support services

Genetic Conditions

Table 2. Common Chromosomal Aneuploidy Syndromes

	Trisomy 21	Trisomy 18	Trisomy 13
Disease	Down syndrome	Edwards syndrome	Patau syndrome
Incidence	1 in 600-800 births Most common abnormality of autosomal chromosomes Rises with advanced maternal age from 1 in 1500 at age 20 to 1 in 20 by age 45	1 in 6000 live births F:M=3:1	1 in 10000 live births
Cranium/Brain	Mild microcephaly, flat occiput, third fontanelle, brachycephaly	Microcephaly, prominent occiput	Microcephaly, sloping forehead, scalp defect, holoprosencephaly
Eyes	Upslanting palpebral fissures, epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus	Microphthalmia, hypotelorism, iris coloboma, retinal anomalies	Microphthalmia, corneal abnormalities
Ears	Low-set, small, overfolded upper helix, frequent acute otitis media, hearing loss	Low-set, malformed	Low-set, malformed
Facial Features	Protruding tongue, large cheeks, low flat nasal bridge, small nose	Cleft lip/palate Small mouth, micrognathia	60-80% cleft lip and palate
Musculoskeletal (MSK)	Short stature Excess nuchal skin Joint hyperflexibility (80%) including dysplastic hips, vertebral anomalies, atlantoaxial instability	Intrauterine growth restriction Clenched fist with overlapping digits, hypoplastic nails, clinodactyly	Small head size Polydactyly
Cardiac Defect	50% (particularly atrioventricular septal defect)	60% (ventricular septal defect, patent ductus arteriosus, atrial septal defect)	80% (atrial septal defect, patent ductus arteriosus, ventricular septal defect)
Gastrointestinal (GI)	Duodenal/esophageal/anal atresia, tracheoesophageal fistula, Hirschsprung's disease, chronic constipation	Hernia, tracheoesophageal fistula	None known
Genitourinary (GU)	Cryptorchidism, rarely fertile	Polycystic kidneys, cryptorchidism	Polycystic kidneys
Central Nervous System (CNS)	Hypotonia at birth Low IQ, developmental delay, hearing problems Onset of Alzheimer's disease in 40s	Hypertonia	Hypo- or hypertonia Seizures, deafness
Other Features	Single transverse palmar crease, clinodactyly, and absent middle phalanx of the 5th finger 1% lifetime risk of leukemia Polycythemia Hypothyroidism	Small for GA Rocker-bottom feet	Single umbilical artery Midline anomalies: scalp, holoprosencephaly, palate, heart, umbilicus, anus
Prognosis/Management	78% 1 yr survival for patients with congenital heart defect, 96% 1yr survival for patients without anomalies Long-term management per AAP Guidelines: Health Supervision of Children with Down Syndrome	13% 1 yr survival, 10% 10 yr survival Profound intellectual disability in survivors	20% 1 yr survival, 13% 10 yr survival Profound intellectual disability in survivors

Table 3. Common Genetic Disorders Involving the Sex Chromosomes

	Fragile X Syndrome	Klinefelter Syndrome	Turner Syndrome
Genotype	CGG trinucleotide repeat expansion in *FMR1* gene on X chromosome; ~55-~200 repeats is considered a premutation, whereas >200 repeats is considered a full mutation	47,XXY (most common) 48,XXXY, 49,XXXXY	45,X0 (50% of cases), 45,X/46,XX mosaic (15% of cases)
Incidence	1 in 3600 males, 1 in 6000 females Most common heritable cause of intellectual disability in males	1 in 1000 live male births Increased risk with advanced maternal age	1 in 2000-2500 live female births No increased risk with advanced maternal age
Phenotype	Overgrowth: macrocephaly, prominent jaw, forehead, and nasal bridge with long and thin face, large protuberant ears, macroorchidism, hyperextensibility, and high arched palate Complications: seizures, scoliosis, mitral valve prolapse Premutation carriers (males more often than females) may demonstrate tremor/ataxia syndrome in later life Female permutation carriers have a higher probability of having a child with FXS, because repeats in the permutation range are more likely to expand to pathogenic repeat length	Tall, slim, underweight No features pre-puberty Post-puberty: variable learning/behavioural difficulties, long limbs, gynecomastia, lack of facial hair	Short stature, short webbed neck, low posterior hairline, wide carrying angle Broad chest, widely spaced nipples Lymphedema of hands and/or feet, cystic hygroma in newborn with polyhydramnios, lung hypoplasia Coarctation of aorta, bicuspid aortic valve Renal and cardiovascular abnormalities, increased risk of hypertension Less severe spectrum with mosaic
IQ and Behaviour	Mild to moderate intellectual disability, 20% of affected males have normal IQ Attention deficit hyperactivity disorder (ADHD) and/or autism Females with full mutation may show milder intellectual impairment Premutation carriers have a normal IQ	Mild intellectual disability or learning difficulties Behavioural or psychiatric disorders: anxiety, shyness, aggressive, and impulsive behaviour acts	Typically normal intelligence
Gonad and Reproductive Function	Premutation carrier females at risk of developing premature ovarian failure	Infertility due to hypergonadotropic hypogonadism	Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics
Diagnosis	Molecular testing of *FMR1* gene: PCR and/or Southern blot analysis of trinucleotide repeat length, methylation analysis	Karyotype	Karyotype

Table 4. Examples of Other Genetic Syndromes

	22q11.2 Deletion Syndrome (DiGeorge syndrome)	Prader-Willi Syndrome	Angelman Syndrome	Noonan Syndrome	CHARGE Syndrome
Genotype	Autosomal dominant; microdeletions of chromosome region 22q11.2	Lack of gene expression on paternal chromosome 15q11-13 due to deletion, maternal uniparental disomy of chromosome 15, or imprinting defect	Lack of gene expression on maternal chromosome 15q11-13 due to deletion, paternal uniparental disomy of chromosome 15, or an imprinting defect Rarely due to pathogenic variants in *UBE3A*	Autosomal dominant with variable expression, pathogenic variants in RAS/MAPK pathway genes ("RASopathies"); autosomal recessive with pathogenic variants in *LZTR1*	2/3 of children with CHARGE have been found to have a pathogenic variant in *CHD7*
Incidence	1 in 4000; second most common genetic diagnosis (next to Down syndrome)	1 in 15000	1 in 10000	1 in 2000	1 in 10000
Clinical Features	**"CATCH 22"** **C**yanotic suggesting congenital heart disease (CHD) **A**nomalies: craniofacial anomalies, micrognathia, and low set ears **T**hymic hypoplasia: immunodeficiency **C**ognitive impairment **H**ypoparathyroidism, hypocalcemia **22**q11 microdeletions High-risk for schizophrenia and other psychiatric disorders	**"H3O"** **H**ypotonia and weakness **H**ypogonadism, obsessive **H**yperphagia **O**besity Short stature, almond-shaped eyes, small hands and feet with tapering of fingers Hypopigmentation, T2DM	Ataxia with severe intellectual disability, seizures, tremulousness, midface hypoplasia, large mouth, fair hair, inappropriately happy demeanour/laughter, fascination with water	Short stature, webbed neck, hypertelorism, low-set ears, epicanthal folds, ptosis, pectus excavatum Right-sided CHD, pulmonary stenosis Increased risk of hematological cancers, cardiomyopathy, moderate intellectual disability, delayed puberty	**"CHARGE"** **C**oloboma **H**eart disease **A**tresia of choanae **R**estriction of growth and mental development **G**U anomalies **E**ar malformations and hearing loss

Table 5. Examples of Familial Cancer Syndromes

Syndrome	Gene	Associated Cancers	Screening and Monitoring
Li-Fraumeni Syndrome	*TP53*	Breast, osteosarcoma, leukemia, soft tissue sarcoma, brain, adrenocortical carcinoma, and numerous other cancers	**Children:** From birth: abdominal/pelvic U/S every 3-4 mo; annual brain MRI and whole-body MRI, if with high-risk TP53 variant **Adults:** Women age 20-75: annual breast MRI Age 18: annual dermatologic examination, abdominal/pelvic U/S, brain MRI, and WBMRI Age 25: colonoscopy and upper endoscopy every 2-5 yr *(Moderate recommendation)*
Lynch Syndrome (HNPCC)	*MSH2, MLH1, MSH6, PMS2, EPCAM*	Colorectal, endometrial, ovarian, renal, pancreatic, liver/biliary duct, stomach, brain, breast	Age 20-25 (or 2-5 yr younger than earliest age of colorectal cancer diagnosis in family): colonoscopy every 1-2 yr Age 30 yr (*MSH6*) and 35 (*PMS2*): colonoscopy every 1-2 yr *(Strong recommendation)*
Familial Adenomatous Polyposis (FAP)	*APC*	Colorectal, small intestine/stomach tumours	Age 10: sigmoidoscopy or colonoscopy every 1-2 yr, colonoscopy once polyps develop *(Strong recommendation)*
Hereditary Breast and Ovarian Cancer Syndrome	*BRCA1, BRCA2*	Female: breast, ovarian, pancreatic Male: prostate, breast, pancreatic	Age 25-65: annual breast MRI Age 30: annual breast MRI and mammograms *(Strong recommendation)*
Von Hippel-Lindau Syndrome	*VHL*	Hemangioblastomas of the brain, spinal cord, and retina; renal cell carcinoma; pheochromocytoma; kidney cysts; pancreatic neuroendocrine tumour; and endolymphatic sac tumour	Age 2: annual physical examination, annual ophthalmologic examination, consider annual catecholamine assessment Consider baseline audiometry at age of school entry Ages 12, 15, and 18: MRI of brain stem, spine, and abdomen, with abdominal U/S in alternating years Age 20: MRI every 2 yr *(Expert opinion)*
Cowden Syndrome	*PTEN*	Breast, thyroid, endometrial	Women: Age 30 (or 5-10 yr before earliest breast cancer in the family): annual mammography Age 30: consider random annual endometrial biopsy and/or U/S Men and Women: At diagnosis: annual thyroid U/S Children: evaluation for neurodevelopmental disorders Age 18: annual comprehensive physical exam Age 30-35: colonoscopy every 5 yr *(Moderate recommendation)*
Neurofibromatosis (NF)			
Type 1	*NF1*	Astrocytoma, optic glioma, neurofibroma, leukemia	Children: evaluation for neurodevelopmental disorders Annual physical exam including evaluation of growth, blood pressure, skin examination, bone examination, neurological examination, and vision screening *(Expert opinion)*
Type 2	*NF2*	Vestibular schwannoma, meningioma, ependymoma, astrocytoma	Annual physical exam including audiology assessment Age 10: annual brain MRI, spinal MRI every 2-3 yr *(Expert opinion)*

Table 6. Examples of Heritable Connective Tissue Disorders

	Loeys-Dietz Syndrome	Classical Ehlers-Danlos Syndrome	Vascular Ehlers-Danlos Syndrome	Marfan Syndrome
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Pathophysiology	Pathogenic variants in *TGFBR1, TGFBR2, SMAD3, TGFB2* genes affecting the TGF-β pathway	Pathogenic variants in *COL5A1* or *COL5A2* genes affecting Type V collagen	Pathogenic variants in *COL3A1* gene that affect Type III collagen, which is most abundant type of collagen in aortic extracellular matrix	Pathogenic variants in *FBN1* gene
Incidence	Unknown	1 in 20000-40000	1 in 100000-250000	1 in 3000-5000
Clinical Features	Vascular findings (aortic aneurysms and dissections, generalized arterial tortuosity), craniofacial features (cleft palate, hypertelorism), skeletal features, easy bruising, allergic/inflammatory disease	Clinical features vary: generalized joint hypermobility, skin hyperextensibility and atrophic scarring, fragile skin, easy bruising, subcutaneous spheroids (fat cysts) on forearms and shins	Arterial fragility and/or rupture, aortic dilatation, intestinal rupture, uterine rupture in pregnancy, characteristic facies (translucent skin, thin lips, pinched nose, prominent ears)	Tall and slender build, disproportionately long limbs and digits, aortic dilatation, lens detachment, pneumothoraces

Table 7. Examples of Intracellular/Extracellular Transport Receptor Disorders

	Hereditary Hemochromatosis	Wilson Disease	CF
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive
Pathophysiology	Pathogenic variants in *HFE* gene (rarely *HJV, HAMP, TFR2*, and *SLC40A1* genes), disrupting regulation of iron	Pathogenic variants in *ATP7B* gene, leading to the impairment of cellular copper transport	Pathogenic variants in *CFTR* gene, which predominantly affects the lungs, but also the GI tract
Incidence	1 in 300	1 in 30000	1 in 3200-15000
Clinical Features	Iron overload (elevated transferrin saturation and ferritin), bronze skin, arthralgia, hormone disturbance (DM, hypogonadism), cirrhosis, cardiomyopathy	Liver disease (acute and/or chronic), movement disorders, psychiatric disturbance, Kayser-Fleischer rings	Severe to mild: Malabsorption, failure to thrive, pancreatic insufficiency Bronchiectasis, male infertility More information found in other chapters*
Management	Phlebotomy for elevated serum ferritin and transferrin saturation	Chelating agents (e.g. penicillamine, trientine)	More information found in other chapters*

*See Respirology, R12 and Pediatrics, P92

Other Single Gene Disorders

SICKLE CELL DISEASE

- autosomal recessive disease caused by pathogenic variants in the HBB gene, resulting in the production of an abnormal version of β-globin and subsequently distorted red blood cells
- see Hematology, H21

DUCHENNE MUSCULAR DYSTROPHY

Incidence

- 1 in 4000 males

Etiology

- one type of muscular dystrophy characterized by progressive skeletal and cardiac muscle degeneration
- X-linked recessive: 1/3 de novo pathogenic variants, 2/3 inherited pathogenic variants
- missing structural protein (dystrophin) → muscle fibre fragility → fibre breakdown → necrosis and degeneration

Clinical Features

- proximal muscle weakness by age 3, positive Gowers' sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy

Diagnosis

- molecular genetic studies of dystrophin gene (*DMD*) (first line)
- genotype-phenotype correlations: different variants in the gene will cause some dystrophin production and a milder muscular dystrophy, Becker muscular dystrophy
- family history (pedigree analysis demonstrating X-linked inheritance)
- increased creatine kinase (50-100x normal) and lactate dehydrogenase
- muscle biopsy, EMG

See Landmark Medical Genetics Trials table for more information on the C-type natriuretic peptide analogue therapy (vosoritide) RCT, which assesses the safety and efficacy of vosoritide in the treatment of achondroplasia in children

Gene Therapy for Spinal Muscular Atrophy (SMA): A Review of Current Challenges and Safety Considerations for Onasemnogene Abeparvovec (Zolgensma)
Cureus 2023;15(3):e36197
Purpose: To review the safety, efficacy, and current challenges of the gene therapy onasemnogene abeparvovec (Zolgensma) in the treatment of the autosomal recessive disorder SMA.
Methods: Narrative literature review of PubMed, MEDLINE, and Ovid databases for articles that provided pertinent information about Zolgensma as a gene therapy for SMA.
Results: 10 articles met the inclusion criteria. There is evidence that Zolgensma is an efficacious therapy for SMA type 1 (the most severe form of the disorder), especially when administered to patients under 3 months of age. Hepatotoxicity is a major concern, but can be managed through close monitoring of liver enzyme levels and prophylactic medications. Zolgensma is more cost-effective than comparable therapies.
Conclusion: Due to its effectiveness, safety profile, and cost, Zolgensma is a good treatment option for SMA type 1. More data is needed to evaluate long-term risks and benefits.

See Landmark Medical Genetics Trials table for more information on the FLAURA trial, which compares Osimertinib against other EGFR inhibitors in patients with EGFR positive NSCLC

Corticosteroids for the Treatment of Duchenne Muscular Dystrophy (DMD)
Cochrane DB Syst Rev 2016;5:CD003725
Purpose: To assess the effects of corticosteroids on prolongation of walking ability, muscle strength, functional ability, and quality of life in DMD and address whether benefit is maintained over long term, assess adverse events, and compare efficacy of different regimens.
Methods: Systematic review including RCTs or quasi-RCTs of corticosteroids given to patients with definitive DMD diagnosis for at least 3 mo.
Results: 12 studies with 667 participants included. Meta-analyses showed that corticosteroids improved muscle strength and function vs. placebo over 6 mo. Evidence from single trials showed 0.75 mg/kg/d superior to 0.3 mg/kg/d on most strength and function measures, with little evidence of further benefit at 1.5 mg/kg/d. Improvements were seen in time taken to rise from the floor, timed walk, four-stair climbing time, ability to lift weights, leg function grade, and forced vital capacity. Moderate quality evidence of adverse effects: excessive weight gain, behavioural abnormalities, cushingoid appearance, and excessive hair growth.
Conclusions: Moderate quality evidence from RCTs indicates that corticosteroid therapy in DMD improves muscle strength and function in the short term (12 mo), and strength (up to 2 yr.) Dose of 0.75 mg/kg/d should be enough. Adverse effects were common but not clinically severe.

Gowers' Sign
Child uses hands to "climb up" the legs to move from a sitting to a standing position. Observed in individuals with weakness of the pelvic and proximal lower limb muscles

Management
- supportive (e.g. physiotherapy, wheelchairs, braces); prevent obesity
- cardiac health monitoring and early intervention (annually if male, every 3-5 years if female)
- bone health monitoring and intervention (vitamin D, bisphosphonates), at baseline and annually
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

Complications
- patient usually wheelchair-bound by age 12
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or CHF in second-third decade

Genetic and Metabolic Investigations for Neurodevelopmental Disorders: Position Statement of the Canadian College of Medical Geneticists (CCMG)
J Med Genet 2023;jmg-2022-108962
Purpose: To provide recommendations for genetic and metabolic investigations for patients with neurodevelopmental disorders (NDD), specifically, patients with global developmental delay (GDD), intellectual disability (ID), and/or autism spectrum disorder (ASD).
Methods: A multidisciplinary group, composed of physicians and clinical scientists, reviewed existing literature and guidelines. Evidence was synthesized and circulated to the CCMG and Canadian Pediatric Society for feedback.
Recommendations:
- chromosomal microarray for patients with GDD, ID, or ASD (first-tier test)
- Fragile X testing for patient with suggestive clinical features or family history (first-tier test)
- metabolic investigations for patients with clinical features suggestive of an inherited metabolic disease
- exome sequencing and comprehensive gene panel for patients with GDD or ID (second-tier test)
- genetic testing is not recommended for patients with NDD in absence of GDD, ID, or ASD, unless accompanied by clinical features suggestive of a syndromic etiology or inherited metabolic disease

Metabolic Diseases

- individually rare but collectively occur in 1 in 1500 births
- inherited disorders of metabolism; most are autosomal recessive
- infants and older children may present with failure to thrive or developmental delay
- organelle disorders can present with dysmorphism
- universal newborn screening in Ontario, Canada includes some treatable metabolic disorders

Table 8. Metabolic Disorders

	Protein Metabolism Disorders	Carbohydrate Disorders	Fatty Acid Disorders	Organelle Disorders
Examples of Conditions	PKU* Tyrosinemia* Homocystinuria* MSUD* Alkaptonuria Propionic acidemia* Urea cycle defects (Ornithine transcarbamylase deficiency)	Galactosemia* GSDs: von Gierke, Pompe, Cori, Andersen, McArdle	MCADD* VLCAD* LCHAD*	Congenital disorders of glycosylation Lysosomal storage diseases: mucopolysaccharidosis (Hunter, Hurler*), Niemann-Pick, Tay-Sachs, Gaucher, Fabry, Krabbe Peroxisomal defects: Zellweger syndrome, X-linked adrenoleukodystrophy
Clinical Manifestations	Coma, irritability, lethargy, poor feeding Seizures Intellectual disability Vomiting and acidosis after feeding initiation Sweet-smelling urine (MSUD)	Hypoglycemia, hepatomegaly, liver failure, cardiomyopathy Growth retardation, failure to thrive	Lethargy, poor feeding Seizures, coma Symptoms triggered by fasting Liver dysfunction Sudden infant death	Progressive neurological problems Developmental regression Chronic encephalopathy Developmental delay Bone crises (Gaucher) Deafness, blindness
Laboratory Findings	Hyperammonemia with normal anion gap (urea cycle defects), hyperammonemia with high anion gap (organic acidemia)	Elevated liver enzymes (galactosemia) Hypoglycemia lactic acidosis hyperlipidemia (GSD)	Hypoketotic hypoglycemia Elevated free fatty acids Elevated creatine phosphokinase	Elevated urine oligosaccharides (oligosaccharidoses) and glycosaminoglycans (mucopolysaccharidoses), abnormal transferrin isoelectric focusing (congenital disorders of glycosylation), abnormal very long chain fatty acids (peroxisomal defects)
Physical Exam	Hypotonia/hypertonia Microcephaly, musty odour, eczema, hypopigmentation (PKU) Dark urine, pigmented sclerae, arthralgias (alkaptonuria) Lens subluxation, Marfanoid appearance (homocystinuria)	Infantile cataracts (galactosemia) Hepatomegaly Muscle weakness/cramping	Hepatomegaly Hypotonia	Dysmorphic facial features Macrocephaly (Lysosomal storage diseases) Hepatosplenomegaly (Niemann-Pick type A/B/C, not Tay-Sachs) Cherry-red spot on macula (Niemann-Pick type A/B, Tay-Sachs, Gaucher) Corneal clouding (Hurler) Infantile cataract (Fabry) Peripheral neuropathy (Fabry, Krabbe) Spasticity

* Metabolic disorders included in Newborn Screening Ontario

Initial Investigations for a Child with Acute Problems Thought to be Due to an Inborn Error of Metabolism
- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, arterial blood gases (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects, and GSDs)
- lactate, ammonium (hyperammonemia with urea cycle defects or organic acidemias), plasma Ca^{2+} and Mg^{2+}, plasma amino acid screen
- routine U/A: ketonuria must be investigated in a neonate, urinary organic acids
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, CSF glycine, free fatty acids (3-β-hydroxybutyrate ratio >4 in fatty acid oxidation defect)

See Landmark Medical Genetics Trials table for more information on the use of Elexacaftor/Tezacaftor/Ivacaftor in children with F508del cystic fibrosis

See Landmark Medical Genetics Trials table for more information on the efficacy and safety of a low-phenylalanine diet in combination with phenylketonuria medical foods or traditional amino acid medical foods in individuals with PKU

Treatment

- varies according to inborn error of metabolism but includes dietary restrictions, toxic metabolite sequestrants, enzyme replacement, etc.
- in the presentation of acute decompensation potentially caused by an inborn error of metabolism, discontinue feeding to prevent further buildup of toxic metabolites

See Landmark Medical Genetics Trials table for more information on the PRISM trial, which evaluates the safety and efficacy of pegvaliase treatment in adults with PKU

Table 9. Presentation and Management of Select Metabolic Disorders

	Phenylketonuria (PKU)	Galactosemia	Maple Syrup Urine Disease (MSUD)	Glycogen Storage Disease (GSD) Type 1 (Von Gierke Disease)	Tay-Sachs Disease	Ornithine Transcarbamylase (OTC) Deficiency
Inheritance and Incidence	1 in 10000; autosomal recessive disease (mutations in *PAH* gene)	1 in 60000; autosomal recessive disease	1 in 185000; autosomal recessive disease (pathogenic variants in *BCKDHA*, *BCKDHB*, and *DBT* genes), 1 in 25000 in Ashkenazi Jewish, 1 in 400 in Mennonites	1 in 100000; autosomal recessive disease, 1 in 20000 in Ashkenazi Jewish	1 in 320000; autosomal recessive disease, 1 in 3600 in Ashkenazi Jewish	1 in 62000 to 77000; X-linked condition
Pathophysiology	Deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to buildup of phenylalanine and its toxic metabolites Mothers who have PKU may have infants with multiple congenital abnormalities	Most commonly due to deficiency of galactose-1-phosphate uridyltransferase leading to an inability to process lactose/galactose	Reduction or elimination of protein complex needed for amino acids leucine, isoleucine, and valine breakdown, leading to toxic build-up	Pathogenic variants in *G6PC* (cause of GSD1a) and *SLC37A4* (cause of GSD1b) genes prevent effective conversion of glucose-6-phosphate to glucose. Glucose-6-phosphate is converted to glycogen and fat which subsequently accumulate in cells, especially in the liver and kidneys	Pathogenic variants in the *HEXA* gene, which encodes alpha subunit of hexosaminidase A; leads to intracellular accumulation of GM2 ganglioside, lysosome dysfunction, and neurodegeneration	Pathogenic variants in the OTC gene, which is localised on the X-chromosome. It encodes an enzyme required for the urea cycle and its dysfunction leads to accumulation of ammonia
Clinical Features	Baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors, and intellectual disability. Hypopigmentation due to low tyrosine levels (fair hair, blue irises)	Signs of liver and renal failure, jaundice, failure to thrive, and cataracts with ingestion of lactose/galactose Complications: Increased risk of sepsis, especially *E. coli* If the diagnosis is not made at birth, liver and brain damage may become irreversible	Feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odour in urine and cerumen May progress to irreversible intellectual disability, hyperactivity, severe failure to thrive, seizures, coma, cerebral edema, and death if inadequately treated	Typically presents between 3-6 mo of age with hepatomegaly, hypoglycemia, poor fasting tolerance, growth failure, and "doll-like" facies (full cheeks with thin extremities) Complications: Lactic acidosis, hyperuricemia, hyperlipidemia, delayed puberty, renal disease, hypoglycemic seizures, hepatic adenomas, osteoporosis	Various presentations: infantile form (onset at 3-6 mo), juvenile form (onset at 2-6 yr), and adult or chronic form (onset at >10 yr) Psychomotor regression, hypotonia, increased startle response, macular cherry red spot, seizures, and hearing impairment	Neonatal onset (male presentation is typically more severe than female presentation): infants appear well at birth, and develop reduced oral intake and lethargy, progressing into tachypnea, hypothermia, severe encephalopathy and a coma Late onset forms: may present at any time and have precipitating event (fasting, illness, protein overload). Lethargy, episodic vomiting, and headaches Complications: seizures, encephalopathy, acute liver failure and a coma
Diagnosis and Management	PKU screening at birth Life-long dietary restriction of phenylalanine starting within the first 10 d of life; especially important during pregnancy to maintain normal phenylalanine levels to prevent maternal PKU effects on fetus Large neutral amino acid (tyrosine) replacement, BH4 enzyme treatment, phenylalanine lyase treatment are other options	Screened for in many newborn screening programs but generally present with liver failure and E. coli sepsis before screening result reported Elimination of galactose from the diet (e.g. dairy, breast milk) Most infants are fed a soy-based diet	MSUD is screened in most newborn screening programs. Serum amino acid evaluation (leucine, isoleucine, alloisoleucine, and valine) and urine organic acid analysis Protein-restricted, high-carbohydrate diet to limit branched amino acid intake A trial of thiamine therapy in addition may be recommended for some infants	Hypoglycemia when interval between feeds are increased (>3-4 h), lactic acidemia, hypertriglyceridemia, and hepatomegaly Treat with nutrition therapy (small frequent feedings, avoid fructose/sucrose/galactose), continuous overnight feedings, raw cornstarch (for slow, sustained glucose release), vitamin supplementation, frequent blood glucose monitoring	Clinical suspicion β-Hexosaminidase enzyme activity (serum) Ashkenazi Jewish carriers often identified by preconception screening Treatment is supportive	Suspect OTCD in patients with hyperammonemia and high urinary orotic acid. Enzyme analysis and/or genetic testing can confirm. Treat with calories (typically 10% dextrose solution at 1.5x maintenance fluids), IV arginine, IV ammonium scavengers (combination of sodium benzoate and sodium phenylbutyrate). Hemodialysis if ammonia >500 umol/L. Long-term: protein restriction supplemented with essential amino acids, citrulline, and ammonia scavengers

See Landmark Medical Genetics Trials table for more information on the SONIA-2 trial, which investigates the efficacy, safety and clinical benefit of nitisinone in the treatment of alkaptonuria

Landmark Medical Genetics Trials

Trial Name	Reference	Clinical Trial Details
PHENYLKETONURIA		
Glycomacropeptide for Nutritional Management of Phenylketonuria: A Randomized, Controlled, Crossover Trial	Am J Clin Nutr 2016; 104(2):334-345	**Title**: Glycomacropeptide for Nutritional Management of Phenylketonuria: A Randomized, Controlled, Crossover Trial **Purpose**: To evaluate the efficacy and safety of a low-phenylalanine (Phe) diet in combination with either glycomacropeptide medical foods (GMP-MFs) or traditional amino acid medical foods (AA-MFs) in individuals with phenylketonuria (PKU). **Methods**: Thirty early-treated individuals aged 15-49 yr with PKU participated in a 2-stage, randomized crossover trial involving consumption of a low-Phe diet with AA-MFs or GMP-MFs for periods of 3 wk each. **Results**: Dietary management of PKU with GMP-MFs compared to AA-MFs resulted in higher intake among participants. GMP-MFs were rated as more acceptable in terms of taste and had less side effects. **Conclusions**: GMP-MFs are safe for dietary management of PKU. GMP-MFs may improve dietary adherence for patients with PKU.
PRISM	Mol Genet Metab 2018; 124(1):27-38	**Title**: Pegvaliase for the Treatment of Phenylketonuria: Results of a Long-Term Phase 3 Clinical Trial Program (PRISM) **Purpose**: Evaluate the efficacy and safety of pegvaliase treatment in adults with phenylketonuria (PKU). **Methods**: Pegvaliase-naive participants with blood Phe >600 µmol/L were randomized to receive 20 mg/d or 40 mg/d of pegvaliase. **Results**: Pegvaliase treatment was given to 261 participants. Within 24 mo, 68.4% of participants achieved blood Phe ≤600 µmol/L. Reductions in blood Phe were associated with neuropsychiatric outcomes, which were maintained with long-term treatment. The vast majority of adverse events (99%) were mild or moderate in severity. **Conclusions**: Results from this trial suggest pegvaliase is safe and efficacious in treating adults with PKU.
CYSTIC FIBROSIS		
Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele	Am J Respir Crit Care Med 2021;203(12):1522	**Title**: Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele **Purpose**: Elexacaftor/tezacaftor/ivacaftor as a combination therapy was effective in treating patients aged greater than 12 years with CF and an accompanying F508del. This 24-week study served to evaluate the efficacy of treatment in patients less than <12 yr. **Methods**: RCT consisting of 66 children aged between 6 and 11 with CF who were assessed for the primary outcome of interest being safety and tolerability of the proposed treatment of oral Elexacaftor 100 mg once daily, Tezacaftor 50 mg once daily, and Ivacaftor 75 mg q12 h for children weighing ≤30 kg and oral Elexacaftor 200 mg once daily, Tezacaftor 100 mg once daily, and Ivacaftor 150 mg q 12 h for children weighing ≤30 kg. Additionally, efficacy of the treatment was also assessed (FEV_1, and Cystic Fibrosis Questionnaire–Revised respiratory domain score). **Results**: Commonly reported side effects included cough, headache, and fever. Treatment also resulted in improvements in predicted FEV_1 (10% improvement), and Cystic Fibrosis Questionnaire-Revised respiratory domain score (7.0 points improvement). **Conclusion**: Results show that treatment of CF with accompanying F508del using Elexacaftor/Tezacaftor/Ivacaftor resulted in significant improvements in patients aged under 12.
NON-SMALL CELL LUNG CANCER		
FLAURA	N Engl J Med 2018; 378(2):113-125	**Title**: Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer (NSCLC) **Purpose**: To compare Osimertinib (a third-generation EGFR inhibitor) against existing standard EGFR inhibitors in patients with previously untreated EGFR mutation-positive NSCLC **Methods**: Double-blind, RCT consisting of 556 previously untreated EGFR mutation positive NSCLC patients. Patients were randomized to receive osimertinib or a standard EGFR-TKI. Outcome of interest included clinician-assessed progression-free survival. **Results**: Median progression-free survival was greater in osimertinib when compared to standard EGFR-TKIs in EGFR mutation positive NSCLC patients (18.9 mo vs. 10.2 mo). **Conclusion**: Results of this study show that osimertinib had superior efficacy when compared to standard EGFR-TKIs.
ALKAPTONURIA		
SONIA-2	Lancet Diabetes Endocrinol. 2020 Sep;8(9):762-772	**Title**: Using Once-Daily Nitisinone for Treatment of Alkaptonuria **Purpose**: No homogentisic acid (HGA) lowering medications have been for treatment of Alkaptonuria. **Methods**: RCT consisting of 138 patients aged 25 or older with confirmed alkaptonuria were randomized to receive either oral nitisinone 10 mg daily or no treatment. The outcome of interest was daily urinary HGA excretion (u-HGA24) after 12 mo. **Results**: 55 patients in the nitisinone group and 53 in the control group completed the study. u-HGA24 at 12 mo was significantly decreased by 99·7% in the nitisinone group compared with the control group. Conclusion: Nitisinone was well tolerated within the treatment group and shows evidence of being an effective treatment for alkaptonuria.
ACHONDROPLASIA		
C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia	N Engl J Med 2019; 378(1):25-35	**Title**: C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia **Purpose**: To assess the efficacy and safety of vosoritide at treating achondroplasia in children **Methods**: RCT consisting of 35 children aged 5 to 14 with achondroplasia. Dosages were stratified based on weight; dose of 2.5 µg per kilogram of body weight (8 patients in cohort 1), 7.5 µg per kilogram (8 patients in cohort 2), 15.0 µg per kilogram (10 patients in cohort 3), or 30.0 µg per kilogram (9 patients in cohort 4). Patients were observed for 24 mo. The outcomes of interest were prevalence of adverse events and growth velocity. **Results**: Each patient experienced minor adverse effects such as pyrexia, hypothermia, erythema, cough, swelling and headaches. 4/35 patients experienced severe adverse effects including grade 3 obstructive sleep apnea, grade 1 tonsillar hypertrophy, grade 3 thyroglossal cyst, and grade 3 syrinx. At 6 mo, there were increases in annualized growth velocity in all cohorts except for that which received 2.5 µg. **Conclusion**: Although associated with mild side effects, with larger scale trials, vosoritide may be used as a treatment for achondroplasia in children.

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MI Medical Imaging

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Acronyms

^{18}FDG	18-fluorodeoxyglucose
ADC	apparent diffusion coefficient
AP	anteroposterior
ARDS	acute respiratory distress syndrome
AV	arteriovenous
BOOP	bronchiolitis obliterans organizing pneumonia
CNS	central nervous system
CT	computed tomography
CTA	computed tomographic angiogram
CVD	collagen vascular disease
CVP	central venous pressure
DDH	developmental dysplasia of the hip
DEXA	dual-energy x-ray absorptiometry
DMSA	dimercaptosuccinic acid
DSA	digital subtraction angiography
DTPA	diethylene triamine pentaacetic acid
DWI	diffusion-weighted image
ECD	ethyl cysteinate dimer
eGFR	estimated glomerular filtration rate
ERCP	endoscopic retrograde cholangio-pancreatography
FLAIR	fluid-attenuated inversion recovery
FNA	fine needle aspiration
GPA	granulomatosis with polyangiitis
HCC	hepatocellular carcinoma
HIDA	hepatobiliary iminodiacetic acid
HMPAO	hexamethylpropyleneamine oxime
HSG	hysterosalpingogram
IBD	inflammatory bowel disease
ICS	intercostal space
ICV	ileocecal valve
IPF	interstitial pulmonary fibrosis
IVP	intravenous pyelogram
KUB	kidneys, ureters, bladder
LA	left atrium
LLL	left lower lobe
LLQ	left lower quadrant
LUL	left upper lobe
LUQ	left upper quadrant
LV	left ventricle
MAA	macroaggregated albumin
MAG3	mertiatide
MCA	middle cerebral artery
MIBG	metaiodobenzylguanidine
MR	magnetic resonance
MRA	magnetic resonance angiogram
MRCP	magnetic resonance cholangiopancreatography
MS	multiple sclerosis
MUGA	multiple gated acquisition
PA	posteroanterior
PBD	percutaneous biliary drainage
PET	positron emission tomography
PFT	pulmonary function test
PICC	peripherally-inserted central catheter
PTA	percutaneous transluminal angioplasty
PTC	percutaneous transhepatic cholangiography
RA	right atrium
RAIU	radioactive iodine uptake
RLL	right lower lobe
RLQ	right lower quadrant
RML	right middle lobe
RUL	right upper lobe
RUQ	right upper quadrant
RV	right ventricle
SPECT	single photon emission computed tomography
SVC	superior vena cava
TIA	transient ischemic attack
TNK	tenecteplase
tPA	tissue plasminogen activator
TPN	total parenteral nutrition
TRUS	transrectal ultrasound
TVUS	transvaginal ultrasound
UPJ	ureteropelvic junction
U/S	ultrasound
VCUG	voiding cystourethrogram
V/Q	ventilation/perfusion

Imaging Modalities

X-Ray Imaging

- x-rays: form of short wavelength electromagnetic energy
- as x-ray photons traverse matter, they can be absorbed (a process known as "attenuation") and/or scattered
- the density of a structure determines its ability to attenuate or "weaken" the x-ray beam
  - air < fat < water < bone < metal
- structures that have high attenuation (e.g. bone) appear white on the resulting images

Plain Films

- x-rays pass through the patient and interact with a detection device (film) to produce a 2-dimensional projection image
- structures closer to the film appear sharper and less magnified
- contraindications: pregnancy (relative)
- advantages: inexpensive, non-invasive, readily available, portable, reproducible, fast, easily read
- disadvantages: radiation exposure (minimal), generally poor at distinguishing soft tissues

Fluoroscopy

- continuous x-rays used for guiding angiographic and interventional procedures, in contrast examinations of the GI tract, and in the OR for certain surgical procedures (e.g. orthopedic, urological)
- on the fluoroscopic image, structures that are radiolucent on plain film appear bright, and structures that are radiopaque on plain film appear dark
- in comparison to continuous fluoroscopy, pulsed fluoroscopy reduces fluoroscopy time and radiation dose
- advantages: real-time visualization of structures
- disadvantages: increased radiation dose compared to plain films

Computed Tomography

- x-ray beam opposite a detector moves in a continuous 360° arc as patient is advanced through the scanner
  - anatomical structures are then reconstructed
- attenuation is quantified in Hounsfield units:
  - windowing and leveling: adjusting the "window width" (range of Hounsfield units displayed) and "window level" (midpoint value of the window width) to maximally visualize certain anatomical structures (e.g. CT chest can be viewed using "lung," "soft tissue," and "bone" settings)
- contraindications: pregnancy (relative), adverse reactions to contrast agents (e.g. previous anaphylaxis allergy, renal failure)
- advantages: delineates soft tissues, excellent at delineating bones and identifying lung/liver masses, may be used to guide biopsies, helical multidetector CT has fast data acquisition and allows 3D reconstruction, CTA is non-invasive compared to conventional angiography for visualization of vasculature
- disadvantages: high radiation exposure, soft tissue characterization is inferior to MRI, some studies require contrast (e.g. IV, oral, rectal), patient anxiety when going through scanner, increased cost and decreased availability compared to plain film, requires expert interpretation of images

Typical Effective Doses from Diagnostic Medical Exposures (in Adults)*

Diagnostic Procedure Type	Equivalent Number of Chest X-Rays	Approximate Equivalent Period of Natural Background Radiation** (~3 mSv/yr)
X-Ray		
Skull	5	12 d
Cervical spine	10	3 wk
Thoracic spine	50	4 mo
Lumbar spine	75	6 mo
Chest (single PA film)	1	2 d
Shoulder	0.5	1 d
Mammography	20	7 wk
Abdomen	35	3 mo
Hip	35	3 mo
Pelvis	30	10 wk
Knee	0.25	<1 d
IV urogram	150	1 yr
Dual-energy x-ray absorptiometry (without/with CT)	0.5/2	<1 d/4 d
Upper GI series	300	2 yr
Small bowel series	200	20 mo
Barium enema	400	2.7 yr
CT		
Head	100	8 mo
Neck	150	1 yr
Spine	300	2 yr
Chest	350	2.3 yr
Chest (pulmonary embolism)	750	5 yr
Coronary angiography	800	5.3 yr
Abdomen	400	2.7 yr
Pelvis	300	2 yr
Radionuclide		
Brain (^{18}FDG)	705	4.7 yr
Bone (^{99m}Tc)	315	2.1 yr
Thyroid (^{99m}Tc)	240	1.6 yr
Thyroid (^{123}I)	95	8 mo
Cardiac rest-stress test		
(^{99m}Tc 1-d)	470	3 yr
(^{99m}Tc 2-d)	640	4 yr
Lung ventilation (^{133}Xe)	25	2 mo
Lung perfusion (^{99m}Tc)	100	8 mo
Renal (^{99m}Tc)	90-165	7-13 mo
Liver-spleen (^{99m}Tc)	105	8.4 yr
Biliary tract (^{99m}Tc)	155	1 yr

*Source: Radiology 2008;248:254-263

**Calculated using average natural background exposure in Canada

Canada.ca: Occupational radiation exposure [Internet]. Government of Canada; [updated 2023 June 2; cited 2023 July 4]. Available from: http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/expos-eng.php

Ultrasound

- high-frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
- reflection (or "echo") occurs when the sound waves reflect off tissue interfaces of different acoustic impedance
- structures are described based on their echogenicity:
  - hyperechoic (echogenic) structures appear bright (U/S reflected) whereas hypoechoic structures appear dark (U/S waves are relatively less reflected with more waves passing through the structure)
  - a simple cyst is anechoic (pure black) as there are no interfaces to produce any echoes
- a gel is used on the skin surface to reduce the difference of impedance between the skin and transducer
- use of higher frequencies on U/S results in greater resolution but poorer penetrance, thus decreased visualization of deeper structures
- artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (e.g. air) or absorbs (e.g. bone) sound waves; enhancement refers to the increase in reflection amplitude (i.e. increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
- duplex scan: grey-scale imaging that utilizes the Doppler effect (sound reflecting off a moving target) to visualize the velocity of blood moving past the transducer
- colour Doppler: assigns a colour based on the direction of blood flow (i.e. red = toward transducer, blue = away)
- advantages: relatively low cost, excellent spatial and soft tissue contrast resolution, non-invasive, no radiation, portable, real-time imaging, may be used for guided biopsies, many different imaging planes (axial, sagittal), differentiates cystic vs. solid
- disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus, poor for bone evaluation, limited field-of-view

Attenuation
Bone (= bright) > grey matter > white matter ("fatty" myelin) > CSF > air (= dark)

Magnetic Resonance Imaging

- imaging technique that uses electromagnetic properties of tissue (mainly water) to produce images in virtually any plane. It does not use ionizing radiation
- patient is placed in a magnetic field generated by electric current; protons, typically from water molecules, align themselves along the direction of magnetization due to their intrinsic polarity; a pulsed radiofrequency beam is subsequently turned on and deflects all the protons off their aligned axes; when the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed; this energy is measured with a detector and interpreted by software to generate MR images
- MR image reflects signal intensity picked up by receiver. Signal intensity is dependent on:
  1. hydrogen density: tissues with low hydrogen density (e.g. cortical bone, lung) generate little to no MR signal compared to tissues with high hydrogen density (e.g. water)
  2. magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment

Remember that water is "**w**hite" on **T2** as "**W**orld **W**ar **II**"

Methods to Reduce the Risk of Contrast-Induced Nephropathy
- Optimal: 0.9% NaCl at 1 mL/kg/h for 12 h pre-procedure and 12 h post-contrast administration
- For same-day procedure: 0.9% NaCl or $NaHCO_3$ at 3 ml/kg/h for 1-3 h pre-procedure and for 6 h post-contrast administration

Table 1. Differences Between Diffusion, T1- and T2-Weighted MR Imaging

Imaging Techniques	Signal Intensity	Main Application	Advantages
Diffusion-Weighted Imaging	Signal intensity dependent on the free molecular motion of water Decreased diffusion is hyperintense (bright), whereas increased diffusion is hypointense (dark)	Neuroradiology	Sensitive for detection of acute ischemic stroke and differentiating an acute stroke from other neurologic pathologies Acute infarction and abscess collections appear hyperintense due to restricted diffusion
T1-Weighted	Fluid is hypointense (dark) and fat is hyperintense (bright)	Body soft tissues	Often considered an anatomic scan since it provides a reference for functional imaging
T2-Weighted	Fluid is hyperintense (bright) and fat is hypointense (dark)	Body soft tissues	Often considered a pathologic scan since it will highlight edematous areas associated with certain pathologies

Positron Emission Tomography Scans

- nuclear tracers are employed to produce images of functional processes in the body
- current generation models integrate PET and CT technologies into a single imaging device (PET-CT) that collects both anatomic and functional information during a single acquisition
- positron-producing radioisotopes, such as 18F, are chemically incorporated into a metabolically active molecule (e.g. glucose); these are then injected into the patient, where they travel to and accumulate in the tissues of interest; as the radioactive substance decays, γ rays are produced, and are detected by the PET scanner

Contraindications to IV Contrast

MADD Failure
Multiple myeloma
Adverse reaction previously
DM
Dehydration
Failure (renal, severe heart)

- contraindications: pregnancy
- advantages: shows metabolism and physiology of tissues (not only anatomic); in oncology, allows for diagnosis, staging, and restaging; has predictive and prognostic value; can evaluate cardiac viability
- disadvantages: cost, ionizing radiation, availability

Contrast Agents

Table 2. Contrast Agents

Imaging Modality	Types	Advantages	Disadvantages	Contraindications
X-Ray	Barium (e.g. oral or rectal)	Radiopaque substance that helps to delineate intraluminal anatomy; may demonstrate patency, lumen integrity, or large filling defects		Previous adverse reaction to contrast; barium enema is contraindicated in toxic megacolon, acute colitis, and suspected perforation
CT	Iodinated agents (routes = oral, rectal, IV)	Delineates intraluminal anatomy; may demonstrate patency, lumen integrity, or large filling defects; under fluoroscopy, may also give information on function of an organ		Previous adverse reaction to contrast, renal failure, DM, pregnancy, multiple myeloma, severe heart failure, and dehydration eGFR <60 may require preventative measures and follow-up
MRI	Gadolinium Chelates	Shortens T1 relaxation time, thereby increasing signal intensity in T1-weighted sequences; highlights highly vascular structures (e.g. tumours)	Risk of nephrogenic systemic fibrosis in patients with end-stage renal disease	Previous adverse reaction to contrast or end-stage renal disease (relative contraindication)
U/S	Microbubbles (IV)	Tiny gas bubbles create many interfaces and appear very echogenic. The microbubbles allow for echo-enhancement of vascular structures or cavities (i.e. echocardiography)		Contraindicated in individuals with right-to-left cardiac shunts or people with known hypersensitivity reactions

FDG PET Imaging in Patients with Pathologically Verified Dementia
J Nucl Med 2000;41(11):1920-28
Purpose: To confirm two beliefs surrounding bilateral temporo-parietal hypometabolism on FDG PET in Alzheimer's disease (AD): (1) it is the metabolic abnormality associated with AD and (2) that sensitivity, specificity, and diagnostic accuracy of this metabolic pattern allows for AD to be differentiated from other degenerative causes of dementia.
Methods: FDG PET scans from 22 individuals with pathologic confirmation of AD diagnosis were visually graded by an experienced nuclear medicine physician to identify classic bilateral temporo-parietal hypometabolism.
Results: Sensitivity, specificity, and diagnostic accuracy of bilateral temporo-parietal hypometabolism for AD were 93%, 63%, and 82%, respectively.
Conclusions: Bilateral temporo-parietal hypometabolism is the classic metabolic abnormality associated with AD. FDG PET may identify this metabolic pattern and can be used clinically to differentiate dementia syndromes.

Chest Imaging

Chest X-Ray

Standard Views

- PA: anterior chest against film plate to minimize magnification of the cardiac silhouette
- lateral: better visualization of retrocardiac space and thoracic spine; more sensitive at detecting small pleural effusions
  - improves localization of lesions when combined with PA view
- AP: alternative to PA view for admitted or acutely ill patients who are unable to tolerate standing or transport; erect or supine; generally a lower quality film than PA because of magnified cardiac silhouette
- lateral decubitus: can help to assess for pleural effusion and pneumothorax; however, POCUS can also be utilized for both of these purposes
- lordotic: angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs on PA and AP views

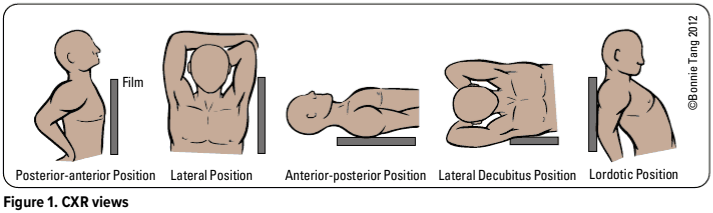


Figure 1. CXR views

Approach to CXR

Basics

- ID: patient name, medical record number (MRN), sex, age
- date of exam
- markers: right and/or left
- technique: view (e.g. PA, AP, lateral), supine or erect
- indications for the study
- comparison: date of previous study for comparison (if available)
- quality of film: inspiration (10 posterior and 7 anterior ribs should be visible), penetration (thoracic spine should be visible), rotation (spinous processes should be equidistant from medial ends of clavicles), magnification (AP films magnify the heart), angulation (clavicles should be S shaped)

Analysis

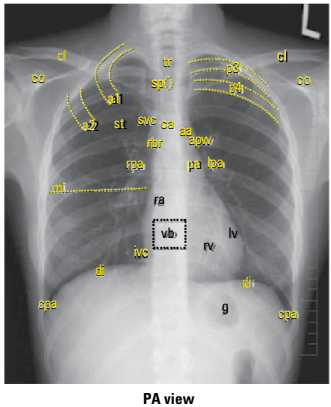
- tubes and lines: check position and be alert for pneumothorax or pneumomediastinum
- soft tissues: neck, axillae, pectoral muscles, breasts/nipples, chest wall
  - nipple markers can help identify nipples (may mimic lung nodules)
  - amount of soft tissue (check for any asymmetry), presence of masses, presence of air (subcutaneous emphysema)
- abdomen (see *Abdominal Imaging, MI11*)
  - free air under the diaphragm, air-fluid levels, distention in small and large bowel
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: cervical spine, thoracic spine, scapulae, ribs, sternum, clavicles, proximal humerus
  - lytic and sclerotic lesions, fractures
- mediastinum: trachea, heart, great vessels
  - cardiomegaly (cardiothoracic ratio >0.5 on PA), tracheal shift, tortuous aorta, widened mediastinum
- hila: pulmonary vessels, mainstem and segmental bronchi, lymph nodes
- lungs: parenchyma, interstitium, pleura, diaphragm
  - abnormal lung opacity, pleural effusions, or thickening
  - right hemidiaphragm usually higher than left due to liver
  - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm
- please refer to Toronto Notes website for supplementary material on how to approach a CXR

Chest X-Ray Interpretation

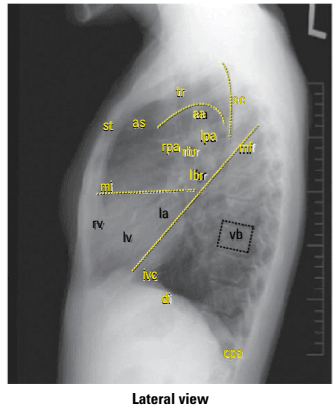
Basics ABCDEF
AP, PA, or other view
Body position/rotation
Confirm name
Date
Exposure/quality
Films for comparison

Analysis ABCDEF
Airways and hilar **A**denopathy
Bones and **B**reast shadows
Cardiac silhouette and **C**ostophrenic angle
Diaphragm and **D**igestive tract
Edges of pleura
Fields (lung fields)

Anatomy



PA view



Lateral view

Legend

a1	anterior 1st rib
a2	anterior 2nd rib
aa	aortic arch
apw	aorto-pulmonary window
as	anterior airspace
ca	carina
cl	clavicle
co	coracoid process
cpa	costophrenic angle
di	diaphragm
g	gastric bubble
ivc	inferior vena cava
la	left atrium
lbr	left mainstem bronchus
lpa	left pulmonary artery
lv	left ventricle
mf	major fissure
mi	minor fissure
p3	posterior 3rd rib
p4	posterior 4th rib
pa	main pulmonary artery
ra	right atrium
rbr	right mainstem bronchus
rpa	right pulmonary artery
rv	right ventricle
sc	scapula
sp	spinous process
st	sternum
svc	superior vena cava
tr	trachea
vb	vertebral body

Figure 2. Location of fissures, mediastinal structures, and bony landmarks on CXR
Note that anterior space is also commonly called retrosternal space

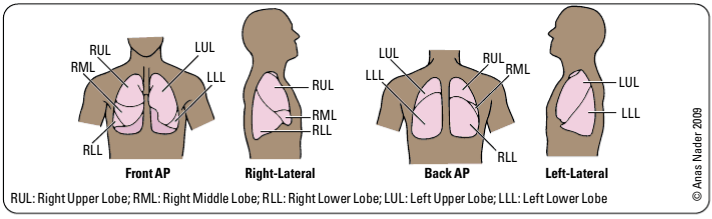


Figure 3. Location of lobes of the lung

Localizing Lesions for Parenchymal Lung Disease

- silhouette sign: when two objects of the same radiodensity abut, they appear indistinguishable on imaging (i.e. the silhouette expected at an anatomical border due to difference in density disappears)
  - can be used to identify lung pathology (consolidation, atelectasis, mass) and localize disease to specific lung segments
- spine sign: on lateral films, vertebral bodies should appear progressively radiolucent (dark) as one moves down the thoracic vertebral column; if they appear more radiopaque, it is an indication of pathology (e.g. consolidation in overlying lower lobe)
- air bronchogram: branching pattern of air-filled bronchi made visible on a background of opacification (i.e. solid or fluid-filled alveoli)

Table 3. Localization Using the Silhouette Sign

Interface Lost	Location of Lung Pathology
SVC/right superior mediastinum	RUL
Right heart border	RML
Right hemidiaphragm	RLL
Aortic knob/left superior mediastinum	LUL
Left heart border	Lingula
Left hemidiaphragm	LLL

Chest Computed Tomography

Approach to CT Chest

- soft tissue window
  - thyroid, chest wall, pleura
  - heart: chambers, coronary artery calcifications, pericardium
  - vessels: aorta, pulmonary artery, smaller vasculature
  - lymph nodes: mediastinal, axillary, hilar
- bone window
  - vertebrae, sternum, ribs: fractures, lytic lesions, sclerosis
- lung window
  - trachea: patency, secretions
  - bronchi: anatomic variants, mucus plugs, airway collapse
  - lung parenchyma: nodules, fibrosis, interstitial changes, consolidation, atelectasis
  - pleural space: effusions, thickening

Table 4. Types of CT Chest

	Advantage	Disadvantage	Contrast	Indication
Standard	Scans full lung very quickly (<1 min) ± high resolution reconstructions	Radiation	±	CXR abnormality Pleural and mediastinal abnormality Lung cancer staging Cancer follow-up Empyema vs. abscess
Low Dose	1/5th the radiation	Decreased detail	No	Lung cancer screening Follow-up infections, lung transplant, metastases
CTA	Iodinated contrast highlights vasculature (scan timed for maximum opacification of vessel being studied)	Contrast can cause severe allergic reaction and can cause acute kidney injury	Yes	PE Aortic aneurysms Aortic dissection

Figure 4. CT thorax windows in axial view

Lung Abnormalities

Atelectasis

- pathogenesis: collapse of lung tissue due to restricted breathing, blockage of bronchi, external compression, or poor surfactant
- findings
  - increased opacity of involved segment/lobe, vascular crowding, silhouette sign, air bronchograms
  - volume loss: fissure displacement, hilar/mediastinal displacement, diaphragm elevation
  - compensatory hyperinflation of remaining normal lung
- differential diagnosis
  - obstructive (most common): alveolar air distal to obstruction is resorbed causing alveolar collapse
    - postsurgical, endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury), or mucous plug (cystic fibrosis)
  - compressive: tumour, bulla, effusion, enlarged heart, lymphadenopathy
  - traction (cicatrization): due to scarring, which distorts alveoli and contracts the lung
  - adhesive: due to lack of surfactant
    - hyaline membrane disease, prematurity
  - passive (relaxation): a result of air or fluid in the pleural space preventing full aeration
    - pleural effusion, pneumothorax
- management: in the absence of a known etiology, persisting atelectasis must be investigated (i.e. CT thorax or bronchoscopy) to rule out bronchogenic carcinoma centrally

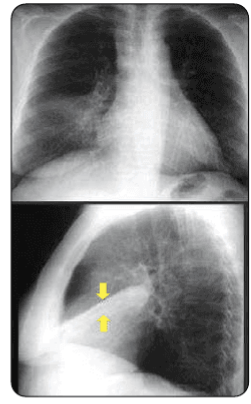


Figure 5. Atelectasis: RML collapse

Consolidation

- pathogenesis: air in alveoli replaced by fluid (transudate, blood), inflammatory exudates, protein, or tumour
- findings
  - air bronchograms: lucent branching bronchi visible through opacification
  - airspace nodules: fluffy, patchy, poorly defined margins with later tendency to coalesce, may take on lobar or segmental distribution
  - silhouette sign
- differential diagnosis
  - fluid: transudate (pulmonary edema), blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
  - inflammatory exudates: bacterial infections, TB, allergic hypersensitivity alveolitis, COP (cryptogenic organizing pneumonia), allergic bronchopulmonary aspergillosis, aspiration, sarcoidosis
  - protein: pulmonary alveolar proteinosis
  - tumour: adenocarcinoma, lymphoma
- management: varies depending on the pattern of consolidation, which can suggest different etiologies; should also be done in the context of clinical picture

DDx of Airspace Disease

- Pus (e.g. infections such as pneumonia)
- Fluid (e.g. pulmonary edema)
- Blood (e.g. pulmonary hemorrhage)
- Cells (e.g. bronchioalveolar carcinoma, lymphoma)
- Protein (e.g. alveolar proteinosis)

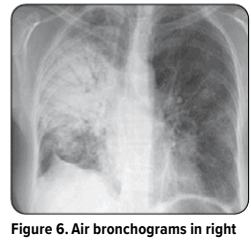


Figure 6. Air bronchograms in right lung

Interstitial Disease

- pathogenesis: pathological process involving pulmonary interstitium (i.e. "lung scaffolding")
- findings
  - septal thickening: fine lines caused by thickened connective tissue septae (most commonly due to pulmonary edema or lymphangitis carcinomatosis)
    - these manifest on CXR as:
      - Kerley A: long thin lines in upper lobes
      - Kerley B: short horizontal lines extending from lateral lung margin
      - Kerley C: diffuse linear pattern throughout lung
  - nodular pattern: 1-5 mm well-defined or ill-defined nodules distributed throughout lung or with a lung zone predominance
    - seen in metastases, pneumoconiosis, granulomatous disease (e.g. sarcoidosis, miliary TB)
  - reticular pattern: fine curvilinear opacities
    - seen in interstitial lung diseases (pulmonary fibrosis)
    - watch for pneumothorax as a complication
  - reticulonodular: combination of reticular and nodular patterns
  - may also see signs of airspace disease (atelectasis, consolidation)
- differential diagnosis
  - occupational/environmental exposure
    - inorganic: asbestosis, coal miner's pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
    - organic: hypersensitivity pneumonitis, bird fancier's lung, farmer's lung (mouldy hay), and other organic dust
  - autoimmune: connective tissue diseases (e.g. rheumatoid arthritis, scleroderma, SLE, polymyositis, mixed connective tissue disease), IBD, celiac disease, vasculitis
  - drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, phenytoin, carbamazepine, fluoxetine, amiodarone, chemotherapy (e.g. methotrexate), immunotherapy, heroin, cocaine, methadone

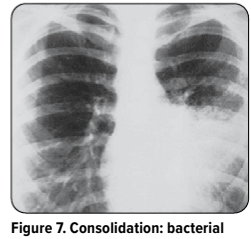


Figure 7. Consolidation: bacterial pneumonia

- infections: TB, non-tuberculous mycobacteria, certain fungal infections, viral infections
- idiopathic: IPF, nonspecific interstitial pneumonia (NSIP), organizing pneumonia
- for causes of interstitial lung disease classified by distribution, see Respirology, R13

• management: high-resolution CT thorax and ± open lung biopsy, multidisciplinary team discussions

Pulmonary Nodule

• findings
- round opacity <3 cm (>3 cm is considered a mass) ± silhouette sign
- note: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers

• differential diagnosis
- extrapulmonary density: nipple, skin lesion, electrode, pleural mass, bony lesion
- solitary nodule
  - tumour: carcinoma, hamartoma, metastasis, bronchial adenoma
  - infection/inflammation: histoplasmoma, tuberculoma, coccidioidomycosis
  - vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, septic embolus
- multiple nodules: metastases, abscess, granulomatous lung disease (TB, fungal, sarcoid, rheumatoid nodules, silicosis, GPA), septic emboli

• management: clinical information and CT appearance determine level of suspicion of malignancy
- if high probability of malignancy, invasive testing (transbronchial or CT-guided transthoracic biopsy) ± PET/CT is indicated
- if low probability of malignancy, follow-up imaging as per Fleischner guidelines 2017

Table 5. Characteristics of Benign and Malignant Pulmonary Nodules

	Malignant	Benign
Margin	Ill-defined/spiculated ("corona radiata")	Well-defined
Contour	Lobulated	Smooth
Calcification	Eccentric or stippled	Diffuse, central, popcorn, concentric
Doubling Time	20-460 d	<20 d or >460 d
Other Features	Cavitation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history	
Size	>3 cm	<3 cm
Cavitation	Yes, especially with wall thickness >15 mm, eccentric cavity, and shaggy internal margins	No
Satellite Lesions	No	Yes

Pulmonary Vascular Abnormalities

Pulmonary Edema

• pathogenesis: fluid accumulation in the airspaces of the lungs

• findings
- vascular redistribution/enlargement, cephalization, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
- fluid initially collects in interstitium
- loss of definition of pulmonary vasculature
- peribronchial cuffing
- Kerley B lines
- reticulonodular pattern

• thickening of interlobar fissures
- as pulmonary edema progresses, fluid collects in alveoli and causes diffuse airspace disease, often in a "bat wing" or "butterfly" pattern in perihilar regions (outermost lung fields tend to be spared)

• differential diagnosis: cardiogenic (e.g. CHF), renal failure, volume overload, non-cardiogenic (e.g. ARDS)

Pulmonary Embolism

• pathogenesis: blockage in the pulmonary arteries due to emboli from pelvic or leg veins, rarely from central venous catheters, air, fat, or amniotic fluid

• findings
- generally not possible to definitively diagnose on plain film; diagnosis made by CT pulmonary angiography or ventilation/perfusion scintigraphy (VQ scan)
- CXR: Westermark sign (localized pulmonary oligemia), Hampton's hump (triangular peripheral infarct), enlarged right ventricle and right atrium, atelectasis, pleural effusion, and rarely pulmonary edema
- definitive imaging study: CT pulmonary angiography to look for filling defect in contrast-filled pulmonary arteries
- VQ scan: can be used in patients with impaired renal function or in pregnancy

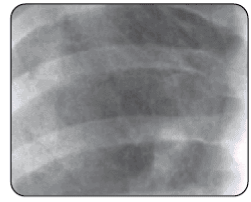


Figure 8. Interstitial disease: fine reticular pattern

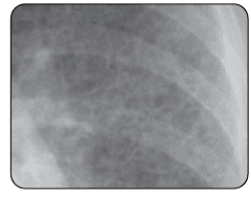


Figure 9. Interstitial disease: medium reticular pattern

DDx of Interstitial Lung Disease

FASSTEN (upper lung disease)
Farmer's lung (hypersensitivity pneumonitis)
Ankylosing spondylitis
Sarcoidosis
Silicosis
TB
Eosinophilic granuloma (Langerhans cell histiocytosis)
Neurofibromatosis

BAD RASH (lower lung disease)
Bronchiolitis obliterans organizing pneumonia (BOOP)
Asbestos
Drugs (nitrofurantoin, hydralazine, isoniazid, amiodarone, many chemotherapy drugs)
Rheumatological disease
Aspiration
Scleroderma
Hamman Rich and idiopathic pulmonary fibrosis (IPF)

DDx for Cavitating Lung Nodule

WEIRD HOLES
Wegener's (GPA)
Embolic (pulmonary, septic)
Infection (anaerobes, pneumocystis, TB)
Rheumatoid (necrobiotic nodules)
Developmental cysts (sequestration)
Histiocytosis
Oncological
Lymphangioleiomyomatosis
Environmental, occupational
Sarcoidosis

Pleural Abnormalities

Pleural Effusion

Table 6. Sensitivity of Plain Film Views for Pleural Effusion

X-Ray Projection	Minimum Volume to Visualize
Lateral decubitus	25 mL: most sensitive
Upright lateral	50 mL: meniscus seen in the posterior costophrenic sulcus
PA	200 mL
Supine	Variable (May appear as diffuse haziness)

- a horizontal fluid level is seen only in a hydropneumothorax (i.e. both fluid and air within pleural cavity)
- effusion may exert mass effect, shift trachea and mediastinum to opposite side, or cause atelectasis of adjacent lung
- U/S is superior to plain film for detection of small effusions and may also aid in thoracentesis; POCUS is now standard of care in acute situations

Pneumothorax

- pathogenesis: gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
- findings
  - upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air
  - more obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiorly)
  - more difficult to detect on supine film; look for the "deep (costophrenic) sulcus" sign, "double diaphragm" sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  - contralateral tracheal and mediastinal shift may occur in tension pneumothorax
- differential diagnosis: spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, central venous catheter insertion, thoracentesis), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung
- management: supplemental oxygen and observation, chest tube insertion in 5th ICS anterior axillary line, or emergent needle decompression in 2nd ICS midclavicular line if tension pneumothorax (followed by chest tube insertion); repeat CXR to ensure resolution

Asbestos

- asbestos exposure may cause various pleural abnormalities including benign plaques (most common; these may calcify), diffuse pleural fibrosis, effusion, and malignant mesothelioma

Mediastinal Abnormalities

Mediastinal Mass

- Felson's method of division outlines three compartments, which provides an approach to the differential diagnosis of a mediastinal mass
- anterior compartment is bordered anteriorly by the sternum and posteriorly by the heart and great vessels
  - 4 Ts: thyroid, thymic neoplasm, teratoma, terrible lymphoma
  - cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
- middle compartment extends from the posterior border of anterior mediastinum to a line 1 cm posterior to the anterior edge of thoracic vertebral bodies
  - esophageal carcinoma, esophageal duplication cyst, metastatic disease, lymphadenopathy (all causes), hiatus hernia, bronchogenic cyst
- posterior border (posterior to the middle line described above)
  - neurogenic tumour (e.g. neurofibroma, schwannoma), neurenteric cyst, thoracic duct cyst, lateral meningocele, Bochdalek hernia, extramedullary hematopoiesis
- any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, or hematoma

Enlarged Cardiac Silhouette

- heart borders
  - on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
  - on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle

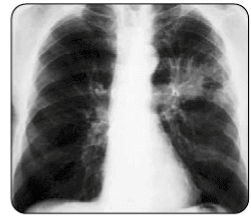


Figure 10. LUL mass: bronchogenic carcinoma

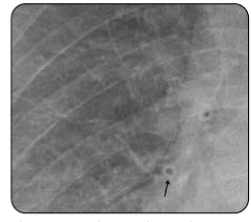


Figure 11. Peribronchial cuffing: interstitial edema

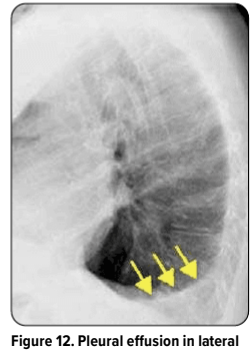


Figure 12. Pleural effusion in lateral view

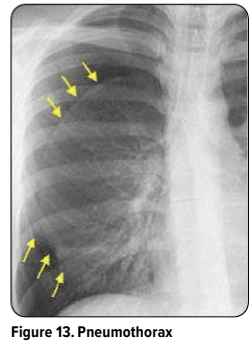


Figure 13. Pneumothorax

- cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
  - using a good quality erect PA chest film in adults, cardiothoracic ratio of >0.5 is abnormal
  - differential of ratio >0.5
    - cardiomegaly (myocardial dilatation or hypertrophy)
    - pericardial effusion
    - poor inspiratory effort/low lung volumes
    - pectus excavatum
  - ratio <0.5 does not exclude enlargement
- pericardial effusion: globular heart with loss of indentations on left mediastinal border
- RA enlargement: increase in curvature of right heart border and enlargement of SVC
- LA enlargement: straightening of left heart border; increased opacity of lower right side of cardiovascular shadow (double heart border); elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film); distance between left main bronchus and "double" heart border >7 cm; splayed carina (late sign)
- RV enlargement: elevation of cardiac apex from diaphragm; anterior enlargement leading to loss of retrosternal air space on lateral; increased contact of right ventricle against sternum
- LV enlargement: rounding of the cardiac apex; displacement of left cardiac border leftward, inferiorly, and posteriorly

Elevated Hemidiaphragm Suggests
PAL DIP
Pregnancy
Atelectasis
Lung resection
Diaphragmatic paralysis
Intra-abdominal process
Pneumonectomy
Pleural effusion also may result in apparent elevation

Depressed Hemidiaphragm Suggests
TALC
Tumour
Asthma
Large pleural effusion
COPD

Tubes, Lines, and Catheters

- ensure appropriate placement and assess potential complications of lines and tubes
- avoid mistaking a line/tube for pathology (e.g. oxygen rebreather mask for pneumothoraces)

Central Venous Catheter
- used for fluid and medication administration, vascular access for hemodialysis, and CVP monitoring
- ideally located at the SVC/atrial junction to prevent inducing arrhythmias or perforating wall of atrium
  - if monitoring CVP, catheter tip must be proximal to venous valves
- tip of well-positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle, and inferiorly by top of RA
- course should parallel that of the SVC; if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- complications: pneumothorax, bleeding (mediastinal, pleural), malposition (artery, pleura), air embolism

Endotracheal Tube
- frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- tip should be located 2-4 cm above tracheal carina (avoids bronchus intubation and vocal cord irritation)
- maximum inflation diameter <3 cm to avoid necrosis of tracheal mucosa and rupture; ensure diameter of balloon is less than tracheal diameter above and below balloon
- complications: aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

Nasogastric Tube
- tip and side port should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- complications: aspiration (parenchymal opacities), pneumothorax

Swan-Ganz Catheter
- to monitor pulmonary capillary wedge pressure and estimate diastolic filling of left heart
- tip should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- if tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture/pseudoaneurysm
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

Chest Tube
- in dorsal and caudal portion of pleural space to evacuate fluid
- in ventral and cephalad portions of pleural space to evacuate pneumothoraces
- tube may lie in fissure as long as functioning
- complications: bleeding, infection, lung laceration

DDx Anterior Mediastinal Mass
4 Ts
Thyroid
Thymic neoplasm
Teratoma
Terrible lymphoma

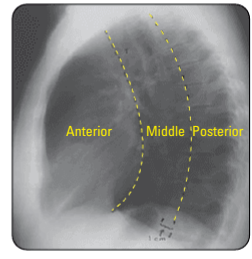


Figure 14. Lateral CXR showing three mediastinal compartments

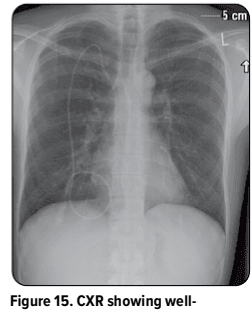


Figure 15. CXR showing well-positioned central venous catheter

Abdominal Imaging

Abdominal X-Ray

3 Views of AXR
Erect/Upright
Supine
Left lateral decubitus

Indications
- acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction, large bowel obstruction
- chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
- not useful in: GI bleeds, chronic anemia, vague GI symptoms

Anatomy
- the abdomen is divided into 2 cavities:
  - peritoneal cavity: lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
  - retroperitoneal cavity: contains several organs situated posterior to the peritoneal cavity; the contour of these can often be seen on radiographs

Table 7. Differentiating Small and Large Bowel

Property	Small Bowel	Large Bowel
Mucosal Folds	Uninterrupted valvulae conniventes (or plicae circulares)	Interrupted haustra extend only partway across lumen
Location	Central	Peripheral (picture frame)
Maximum Diameter	3 cm	6 cm (9 cm at cecum)
Maximum Fold Thickness	3 mm	5 mm
Other	Rarely contains solid fecal material	Commonly contains solid fecal material

3-6-9 Rule of Dilation
Small bowel (>3 cm)
Large bowel (>6 cm)
Cecum (>9 cm)

Approach to Abdominal X-Ray
- mnemonic: "Free ABDO"
- "Free": free air and fluid
  - free fluid
    - small amounts of fluid: increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
    - large amounts of fluid: diffuse increased opacification on supine film; bowel floats to centre of anterior abdominal wall
    - ascites and blood (hemoperitoneum) are the same density on the radiograph and cannot be differentiated
  - free intraperitoneal air suggests rupture of a hollow viscus (anterior duodenum, transverse colon, etc.), penetrating trauma, or recent (<7 d) surgery
- "A": air in the bowel (can be normal, ileus, or obstruction)
  - volvulus – twisting of the bowel upon itself resulting in obstruction; from most to least common:
    1. sigmoid: massively dilated sigmoid projects to right or mid-upper abdomen with proximal dilation ("coffee bean" sign)
    2. cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
    3. gastric: rare
    4. transverse colon: rare (usually in younger individuals)
    5. small bowel: "corkscrew" sign (rarely diagnosed on plain films, seen best on CT)
  - toxic megacolon
    - manifestation of fulminant colitis
    - extreme dilatation of colon (>6.5 cm) with mucosal changes (e.g. foci of edema, ulceration, pseudopolyps) and loss of normal haustral pattern
- "B": bowel wall thickening
  - increased soft tissue density in bowel wall, thumb-like indentations in bowel wall ("thumb-printing"), or a picket-fence appearance of the valvulae conniventes ("stacked coin" appearance)
  - may be seen in IBD, infection, ischemia, hypoproteinemic states, and submucosal hemorrhage
- "D": densities
  - bones: look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
  - abnormal calcifications: approach by location
    - RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
    - RLQ: ureteral stone, appendicolith, gallstone ileus
    - LUQ: renal stone, adrenal calcification, tail of pancreas
    - LLQ: ureteral stone
    - central: aorta/aortic aneurysm, pancreas, lymph nodes
    - pelvis: phleboliths (i.e. calcified veins), uterine fibroids, bladder stones
- "O": organs
  - kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
  - outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)

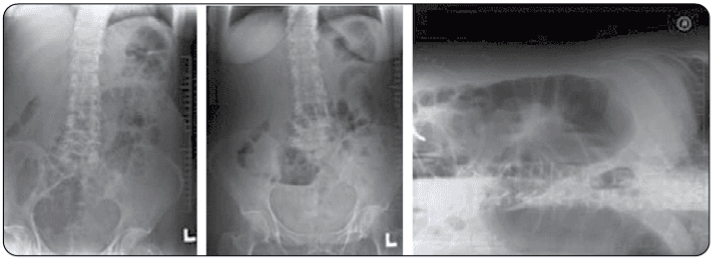


Figure 16. Normal AXRs: (left) supine anteroposterior AXR, (middle) upright anteroposterior AXR, and (right) left lateral decubitus AXR

Table 8. Abnormal Air on Abdominal X-Ray

Air	Appearance	Common Etiologies
Extraluminal Intraperitoneal (pneumoperitoneum)	Upright film: air under diaphragm Left lateral decubitus film: air between liver and abdominal wall Supine film: gas outlines of structures not normally seen: Inner and outer bowel wall ("Rigler's" sign) Falciform ligament Peritoneal cavity ("football" sign)	Perforated viscus Postoperative (up to 10 d to be resorbed)
Retroperitoneal	Gas outlining retroperitoneal structures allowing increased visualization: Psoas shadows Renal shadows	Perforation of retroperitoneal segments of bowel: duodenal ulcer, post-colonoscopy
Intramural (pneumatosis intestinalis)	Lucent air streaks in bowel wall, 2 types: 1. Linear 2. Rounded (cystoides type)	1. Linear: ischemia, necrotizing enterocolitis 2. Rounded/cystoides (generally benign): primary (idiopathic), secondary (COPD)
Intraluminal	Dilated loops of bowel, air-fluid levels	Adynamic (paralytic) ileus, mechanical bowel obstruction
Loculated	Mottled, localized in abnormal position without normal bowel features	Abscess
Biliary	Air centrally over liver	Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis
Portal Venous	Air peripherally over liver in branching pattern	Bowel ischemia/infarction

Table 9. Adynamic Ileus vs. Mechanical Obstruction

Feature	Adynamic Ileus	Mechanical Obstruction
Calibre of Bowel Loops	Normal or dilated	Usually dilated
Air-Fluid Levels (erect and left lateral decubitus films only)	Same level in the same single loop	Multiple air fluid levels giving "step ladder" appearance, dynamic (indicating peristalsis present), "string of pearls" (row of small gas accumulations in the dilated valvulae conniventes)
Distribution of Bowel Gas	Air throughout GI tract is generalized or localized In a localized ileus (e.g. pancreatitis, appendicitis), dilated "sentinel loop" remains in the same location on serial films, usually adjacent to the area of inflammation	Dilated bowel up to the point of obstruction (i.e. transition point) No air distal to obstructed segment "Hairpin" (180°) turns in bowel

Abdominal Computed Tomography

- indications for plain CT: renal colic, hemorrhage
- indications for CT with contrast:
  - IV contrast given immediately before or during CT to allow identification of arteries and veins
    - portal venous phase: indicated for majority of cases
    - biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumours
    - caution: contrast allergy (may pre-medicate with steroids and antihistamine)
    - contraindication: impaired renal function (eGFR <30 mL/min/1.73 m ^{2})
  - oral contrast: barium or water-soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
  - rectal contrast: given for investigation of colonic lesions

Biliary vs. Portal Venous Air
"Go with the flow": air follows the flow of bile or portal venous blood
Biliary air is most prominent centrally over the liver
Portal venous air is most prominent peripherally

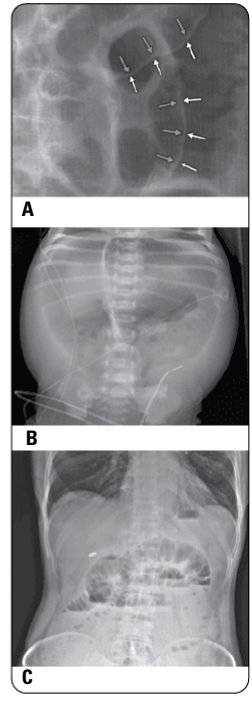


Figure 17. (A) "Rigler's" sign (B) "football" sign (C) "string of pearls" sign
Rigler's sign courtesy of Dr Jeremy Jones, Radiopedia.org, rID: 8041. Prof Frank Gaillard https://radiopedia.org/cases/8041
Football sign courtesy of Dr Maxime St-Amant, Radiopedia.org, rID: 18597. https://radiopedia.org/cases/18597
String of pearls courtesy of Dr Maulik S Patel, Radiopedia.org, rID: 14006. https://radiopedia.org/cases/14006

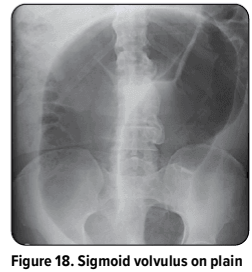


Figure 18. Sigmoid volvulus on plain film, "coffee bean" sign
Courtesy of Dr Henry Knipe, Radiopedia.org, rID: 28620. https://radiopedia.org/cases/28620

Approach to Abdominal Computed Tomography

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ or structure individually, from top to bottom, evaluating the size and shape of each area of increased or decreased density
- evaluate the following:
  - soft tissue window
    - liver, gallbladder, spleen, and pancreas
    - adrenals, kidneys, ureters, and bladder
    - stomach, duodenum, small bowel mesentery, and colon/appendix
    - retroperitoneum (aorta, vena cava, and mesenteric vessels; look for adenopathy in vicinity of vessels)
    - peritoneal cavity for fluid or masses
    - abdominal wall and adjacent soft tissue
  - lung window
    - visible lung (bases)
  - bone window
    - vertebrae, spinal cord, and bony pelvis

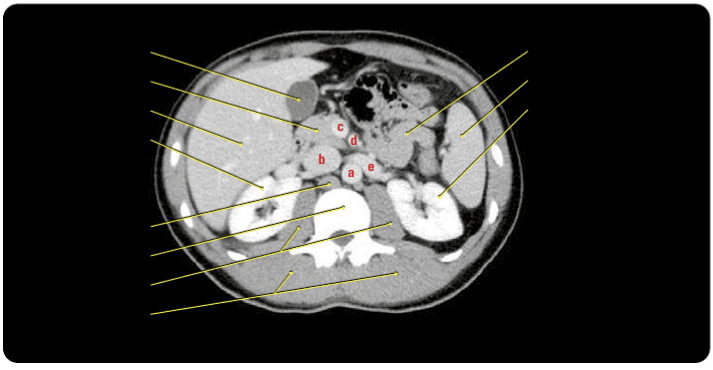


Figure 19. Axial abdominal computed tomography

CT and Bowel Obstruction

- cause of bowel obstruction is rarely found on plain films; CT is the best imaging modality
- the "3,6,9" rule is a very useful guide for determining when the bowel is dilated; the maximum diameter for the small bowel is 3 cm, for large bowel is 6 cm, and for cecum is 9 cm; this can also be useful to distinguish small and large bowel, and to assess for 'impending' cecal perforation (e.g. post-untreated Ogilvie's syndrome)
- closed-loop obstruction: an obstruction in two locations (usually small bowel) creating a loop of bowel obstructed both proximally and distally; complications (e.g. ischemia, perforation, necrosis) may occur quickly

CT Colonography (Virtual Colonoscopy)

- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumours)
- two CT scans of the abdomen (prone and supine) after the instillation of carbon dioxide into a prepped colon
- computer reconstruction of 2D CT images into a 3D intraluminal view of the colon
- lesions seen on 3D images correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, or staging of obstructing colonic lesions

Contrast Studies

Table 10. Types of Contrast Studies

Study	Organ	Procedure Description	Assessment	Findings
Cine Esophagogram	Cervical esophagus	Contrast agent swallowed Recorded for later playback and analysis	Dysphagia, swallowing incoordination, recurrent aspiration, postoperative cleft palate repair	Aspiration, webs (partial occlusion), Zenker's diverticulum, cricopharyngeal bar, laryngeal tumour
Barium Swallow	Thoracic esophagus	Contrast agent swallowed under fluoroscopy, selective images captured	Dysphagia, rule out GERD, post-esophageal surgery	Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear
Upper GI Series	Thoracic esophagus, stomach, and duodenum	Double contrast study: 1. Barium to coat mucosa 2. Gas pills for distention Patient NPO after midnight	Dyspepsia, investigate possible upper GI bleed, weight loss/anemia, post-gastric surgery	Ulcers, neoplasms, filling defects
Enterography and Enteroclysis (MRI or CT)	Entire small bowel	Enterography: patient drinks 1-2 L of sorbitol, psyllium, or barium solution to distend small bowel Enteroclysis: NJ tube used to pump barium, psyllium, or sorbitol contrast media directly into small bowel	IBD, malabsorption, weight loss/anemia, Meckel's diverticulum	Neoplasms, IBD, malabsorption, infection

Colorectal Cancer: CT Colonography and Colonoscopy for Detection-Systematic Review and Meta-Analysis
Radiology 2011;259:393-405
Purpose:To assess the sensitivity of computed tomography colonography (CTC) and optical colonoscopy (OC) for colorectal cancer (CRC) detection.
Methods: Systematic review and meta-analysis of diagnostic studies evaluating CTC detection of CRC based on a priori eligibility criteria, in particular requiring both OC and histological confirmation of disease. Studies that also assessed true-positive and false-negative diagnoses with OC were used to calculate OC sensitivity. Sensitivity of CT colonography and OC for CRC was the main outcome.
Results: 49 studies on 11,151 patients undergoing diagnostic study for detection of CRC were included. CTC has a sensitivity of 96.1% (95% CI 93.8%, 97.7%) and OC has a sensitivity of 94.7% (95% CI 90.4%, 97.2%) for the detection of CRC.
Conclusion: CTC is highly sensitive for the detection of CRC and may be a better modality for the initial investigation of suspected CRC, assuming reasonable specificity.

Specific Visceral Organ Imaging

- for the management of urgent and emergent peritoneal masses

Liver

- U/S: assessment of cysts, abscesses, tumours, biliary tree
- CT ± IV: most popular procedure for imaging the liver parenchyma (primary liver tumours, metastases, cysts, abscesses, trauma, cirrhosis)
- MRI: excellent in evaluation of primary liver tumours, liver metastases, other parenchymal conditions; particularly helpful in differentiating common benign hepatic hemangiomas from primary liver tumours and metastases
- elastography: measures shear wave velocity by U/S (FibroScan) or MRI (MR elastography) to non-invasively quantify liver fibrosis
- findings:
  - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
  - porto-systemic shunts: caput medusae, esophageal varices, spontaneous spleno-renal shunt
  - U/S: cirrhosis appears nodular and hyperechoic with irregular areas of atrophy of the right lobe and hypertrophy of the caudate or left lobes
  - CT: fatty infiltration appears hypodense
- some masses require contrast to be visualized
- upon identifying a liver lesion on imaging (e.g. U/S), the follow-up imaging modality should be CT or MRI. CT would be four-phase non-contrast, arterial, venous, and delayed to distinguish the common benign liver lesion hemangioma from other tumours

Spleen

- U/S, CT, nuclear medicine scan (nuclear medicine only to distinguish ectopic splenic tissue from enhancing tumours)
- CT for splenic trauma (hemorrhage)

See Landmark Medical Imaging Trials table for more information on the AMACING trial comparing hydration to no hydration in the incidence of contrast-induced nephropathy.

Normal liver appears more dense than spleen on CT. If less dense, suspect fatty infiltration

Liver Mass DDx

5 Hs
HCC
Hydatid cyst
Hemangioma
Hepatic adenoma
Hyperplasia (focal nodular)

Table 11. Imaging of Liver Masses

	U/S	CT
Benign Mass		
Hepatic Adenoma	Well-defined mass with hyperechoic areas due to hemorrhage	Well-defined hypervascular lesion with enlarged central vessel becoming slightly isoattenuating in venous phase
Hemangioma	Homogeneous hyperechoic mass	Peripheral globular enhancement in arterial phase scans; central filling and persistent enhancement on delayed scans
Focal Nodular Hyperplasia	Well-defined mass, central scar seen in 50% of cases	Hypervascular mass in arterial phase and isoattenuation to liver in portal venous phase
Abscess	Ill-defined, irregular margin, hypoechoic contents	Low attenuation lesion with an irregular enhancing wall
Hydatid Cyst	Simple/multiloculated cyst	Low attenuation simple or multiloculated cyst; calcification
Malignant Mass		
HCC	Single/multiple masses, or diffuse infiltration	Hypervascular; enhances in arterial and washes out in venous phase with portal venous tumour thrombus
Metastases	Multiple masses of variable echotexture	Usually low attenuation on contrast-enhanced scan

Pancreas

- tumours
  - U/S: mass is more echogenic than normal pancreatic tissue
  - CT: preferred modality for diagnosis/staging
- ductal dilation secondary to stone/tumour
  - MRCP: imaging of ductal system using MRI cholangiography; no therapeutic potential
  - ERCP: endoscopic injection of dye into the biliary tree and x-ray imaging to assess pancreatic and biliary ducts; therapeutic potential (stent placement, stone retrieval)
    - acute pancreatitis is a complication in 5% of diagnostic procedures and 10% of therapeutic procedures

Biliary Tree

- U/S: bile ducts usually visualized only if dilated, secondary to obstruction (e.g. choledocholithiasis, benign stricture, mass)
- CT: dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- MRCP, ERCP, PTC: further evaluation of obstruction and possible intervention

"itis" Imaging

Acute Cholecystitis

- pathogenesis: inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct, or in the case of acalculous cholecystitis, due to gallbladder ischemia or cholestasis (see General and Thoracic Surgery, GS56)
- best imaging modality: U/S (best sensitivity and specificity); nuclear medicine (HIDA scan) can help diagnose cases of acalculous or chronic cholecystitis
- findings: most sensitive findings are presence of gallstones and positive sonographic Murphy's sign (tenderness from pressure of U/S probe over visualized gallbladder). Secondary findings include thickened gallbladder wall (>3 mm), dilated gallbladder, and pericholecystic fluid
- management: admit, NPO, IV fluids, analgesia, cefazolin, and early laparoscopic cholecystectomy

Acute Appendicitis

- pathogenesis: luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess or peritonitis (see General and Thoracic Surgery, GS35)
- best imaging modality: U/S or CT
- findings:
  - U/S: thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible; may also demonstrate signs of other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
  - CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage
- management: admit, NPO, IV fluids, analgesia, cefazolin + metronidazole, and appendectomy

Acute Diverticulitis

- pathogenesis: erosion of the intestinal wall (most commonly rectosigmoid) by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro- or macroscopic perforation (see General and Thoracic Surgery, GS39)
- best imaging modality: CT, although U/S is sometimes used
- contrast: oral and rectal contrast given before CT to opacify bowel

Revised Estimates of Diagnostic Test Sensitivity and Specificity in Suspected Biliary Tract Disease
Arch Intern Med 1998;154:2573-2581
Purpose: To assess the sensitivity and specificity of tests used to diagnose cholelithiasis and acute cholecystitis, including U/S, oral cholecystography, radionucleotide scanning with Technetium, MRI, or CT.
Methods: Meta-analysis of studies evaluating the use of different imaging modalities in the diagnosis of biliary tract disease. Main outcomes were sensitivity and specificity of the different imaging modalities, using the gold standard of surgery, autopsy, or 3 mo clinical follow-up for cholelithiasis. For acute cholecystitis, pathologic findings, confirmation of an alternate disease, or clinical resolution during hospitalization for cholecystitis were used as the standard.
Results: Thirty studies were included. For evaluating cholelithiasis, U/S had the best unadjusted sensitivity (0.97; 95% CI 0.95-0.99) and specificity (0.95, 0.88-1.00) and adjusted (for verification bias) sensitivity (0.84; 0.76-0.92) and specificity (0.99; 95% CI 0.97-1.00). For evaluating acute cholecystitis, radionucleotide scanning has the best sensitivity (0.97; 0.96-0.98) and specificity (0.90; 0.86-0.95).
Conclusion: U/S is the test of choice for diagnosing cholelithiasis and radionucleotide scanning is the superior test for diagnosing acute cholecystitis.

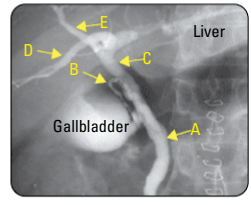


Figure 20. ERCP: biliary tree (A) common bile duct (B) cystic duct (C) common hepatic duct (D) right hepatic duct (E) left hepatic duct

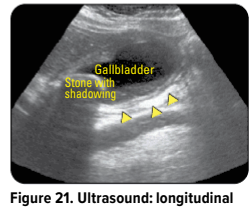


Figure 21. Ultrasound: longitudinal view of an inflamed gallbladder Arrowheads show thickened walls and pericholecystic fluid

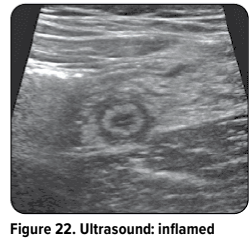


Figure 22. Ultrasound: inflamed appendix

- findings:
  - cardinal signs: thickened wall, mesenteric infiltration, gas-filled diverticula, abscess
  - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
  - sometimes difficult to distinguish from perforated cancer (send abscess fluid for cytology and follow up with colonoscopy)
  - if chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)
- management: ranges from antibiotic treatment to surgical intervention; can use imaging to follow progression

Acute Pancreatitis
- pathogenesis: activation of proteolytic enzymes within pancreatic cells leading to local and systemic inflammatory response (see Gastroenterology, G48); a clinical/biochemical diagnosis
- best imaging modality: imaging used to support diagnosis and evaluate for complications (diagnosis cannot be excluded by imaging alone)
  - U/S good for screening and follow-up
  - CT is useful in advanced stages and in assessing for complications (1st line imaging test)
- findings:
  - U/S: hypoechoic enlarged pancreas (if ileus present, gas obscures pancreas)
  - CT: enlarged pancreas, edema, fat stranding with indistinct fat planes, mesenteric and Gerota's fascia (renal fascia) thickening, pseudocyst in lesser sac, abscess (gas or thick-walled fluid collection), pancreatic necrosis (low attenuation gas-containing non-enhancing pancreatic tissue), hemorrhage
- management: supportive therapy
  - CT-guided needle aspiration and/or drainage of abscess when clinically indicated
  - pseudocyst may be followed by CT and drained if symptomatic

Chronic Pancreatitis
- pathogenesis: (see Gastroenterology, G50)
- best imaging modality: MRCP (can show calcification and duct obstruction)
- findings: U/S, CT scan, and MRI may show calcifications, ductal dilatation, enlargement of the pancreas, and fluid collections (e.g. pseudocysts) adjacent to the gland

Angiography of Gastrointestinal Tract

- anatomy of the arterial branches of the GI tract
  - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
  - superior mesenteric artery: jejunal, ileal, ileo-colic, right colic, middle colic
  - inferior mesenteric artery: left colic, superior rectal
- imaging modalities
  - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
    - flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
  - CT angiogram: modality of choice, non-invasive using IV contrast (no catheterization required)

Genitourinary System and Adrenal

Urological Imaging

Kidney, Ureter, and Bladder (KUB) X-Ray
- a frontal supine radiograph of the abdomen
- indication: useful in evaluation of radiopaque renal stones (exceptions: uric acid and indinavir stones), indwelling ureteric stents/catheters, and foreign bodies in abdomen
- findings: addition of IV contrast excreted by the kidney (intravenous urogram) allows better visualization of the urinary tract but has been largely replaced by CT urography

Abdominal CT

Renal Masses
- Bosniak classification for cystic renal masses
- class I-II: benign and can be disregarded
- class IIF: should be followed
- class III-IV: suspicious for malignancy, requiring additional workup

Computed Tomography and Ultrasonography to Detect Acute Appendicitis in Adults and Adolescents
Ann Intern Med 2004;141:537-546
Purpose: To review the diagnostic accuracy of CT and U/S in the diagnosis of acute appendicitis.
Methods: Meta-analysis of prospective studies evaluating the use of CT or U/S, followed by surgical or clinical follow-up in patients with suspected appendicitis. Patients ≥14 yr with a clinical suspicion of appendicitis were eligible. Sensitivity and specificity using surgery or clinical follow-up as the gold standard were the main outcomes studied.
Results: Twenty-two studies were included. CT (12 studies) had an overall sensitivity of 0.94 (95% CI 0.91-0.95) and a specificity of 0.95 (0.93-0.96). U/S (14 studies) had an overall sensitivity of 0.86 (0.83-0.88) and a specificity of 0.81 (0.78-0.84).
Conclusion: CT is more accurate for diagnosing appendicitis in adults and adolescents, although verification bias and inappropriate blinding of reference standards were noted in the included studies.

Ultrasound, Computed Tomography or Magnetic Resonance Imaging for Acute Appendicitis in Children
Pediatr Radiol 2017;47:186-196
Purpose: Compare the accuracies of U/S, CT, and MRI for clinically suspected acute appendicitis in children.
Methods: Search and meta-analysis. The sensitivity, specificity, and the area under the curve of summary receiver operating characteristics were calculated and compared.
Results: 19 studies of U/S, 6 studies of CT, and 4 studies of MRI. The analysis showed that the area under the receiver operator characteristics curve of MRI (0.995) was a little higher than that of US (0.987) and CT (0.982; P>0.05).
Conclusion: US, CT, and MRI have high diagnostic accuracies of clinically suspected acute appendicitis in children overall with no significant difference.

Angiography requires active blood loss
1-1.5 mL/min under optimal conditions for a bleeding site to be visualized in cases of lower GI bleeding

Imaging Modality Based on Presentation
Acute testicular pain = Doppler, U/S
Amenorrhea = U/S, MRI (brain)
Bloating = Plain film/CT (if abnormal)
Flank pain = U/S, CT
Hematuria = U/S, Cystoscopy, CT
Infertility = HSG, MRI
Lower abdominal mass = U/S, CT
Lower abdominal pain = U/S, CT
Renal colic = U/S, KUB, CT
Testicular mass = U/S
Urethral stricture = Urethrogram

Table 12. Bosniak Classification for Cystic Renal Masses

Classes	Definition
Simple Renal Cysts	
Class I	Fluid-attenuating well-defined lesion, no septation, no calcification, no solid components, hairline thin wall
Class II	Same as class I + fine calcification or moderately thickened calcification in septae or walls; also includes hyperdense cysts (<3 cm) that do not enhance with contrast
	*Class IIF: multiple hairline-thin septa with minimal thickening, no enhancing soft tissue components, completely intrarenal non-enhancing high-attenuating renal lesions >3 cm
Complex Renal Cysts	
Class III	Thick irregular walls ± calcifications ± septated, enhancing walls, or septa with contrast
Renal Cell Carcinoma	
Class IV	Same as class III + soft tissue enhancement with contrast (defined as >10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase ± areas of necrosis

- plain CT KUB indications: general imaging of renal anatomy, renal colic symptoms, assessment of renal calculi (size and location) and potential sequelae (infection and obstruction), and hydronephrosis prior to urological treatment
- CT urography indications: investigation of cause of hematuria, detailed assessment of urinary tracts (excretory phase), high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts, assessment of renal calculi
  - phases: unenhanced, excretory
- renal triphasic CT indications: standard imaging for renal masses, allows accurate assessment of renal arteries and veins, better characterization of suspicious renal masses – especially in differentiating renal cell carcinoma from more benign masses, and preoperative staging
  - phases: unenhanced, arterial and venous (nephrographic), excretory

Ultrasound

- indications: initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic masses, simple vs. complicated cysts); modality of choice for screening patients with suspected hydronephrosis (no IV contrast injection, no radiation exposure, and can be used in patients with renal failure); TRUS useful to evaluate prostate gland and guide biopsies; Doppler U/S to assess renal vasculature
- findings: solid renal masses are echogenic (bright on U/S), cystic renal masses have smooth well-defined walls with anechoic interior (dark on U/S), and complicated cysts have internal echoes within a thickened, irregular wall

Retrograde Pyelography

- indications: visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium, visualized by radiography or fluoroscopy; ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction, or allergy to IV contrast)
- findings: only yields information about the collecting systems (renal pelvis and associated structures), no information regarding the parenchyma of the kidney

Voiding Cystourethrogram

- bladder filled with contrast to the point where voiding is triggered
- fluoroscopy (continuous, real-time x-ray) to visualize bladder during voiding
- indications: males or young females with recurrent UTIs, hydronephrosis, hydroureter, suspected lower urinary tract obstruction, suspected bladder trauma, or vesicoureteral reflux
- findings: evaluation of bladder contractility and evidence of vesicoureteral reflux

Retrograde Urethrogram

- a small Foley catheter placed into penile urethral opening, followed by instillation of contrast and radiographic imaging
- indications: used mainly to study strictures or trauma to the male urethra; first-line study if signs of urethral injury are present (i.e. trauma with blood at the urethral meatus, scrotal hematoma, or high-riding prostate)

MRI

- advantages: better contrast resolution and tissue discrimination, lack of exposure to ionizing radiation, safer contrast, ability to obtain imaging directly from multiple planes (coronal, sagittal, oblique)
- indications: indicated over CT for depiction of renal masses in patients with previous nephron-sparing surgery, patients requiring serial follow-up (less radiation dosage), patients with reduced renal function, patients with solitary kidneys, clinical staging of prostate cancer (endorectal coil MRI)

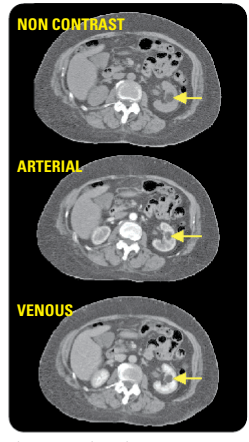


Figure 23. Triphasic CT of an angiomyolipoma: showing fat density with non-contrast scan, mildly enhancing with contrast

Ultrasonography vs. Computed Tomography for Suspected Nephrolithiasis
NEJM 2014;371:1100-1110
Purpose: Investigate whether the initial imaging method for patients with suspected nephrolithiasis should be CT or U/S.
Methods: Multicenter, pragmatic, comparative effectiveness trial, randomly assigned patients in the ED with suspected nephrolithiasis to undergo initial diagnostic ultrasonography performed by an emergency physician (POCUS), U/S performed by a radiologist, or abdominal CT. Comparisons: 30 d incidence of high-risk diagnoses with complications that could be related to missed or delayed diagnosis and the 6 mo cumulative radiation exposure.
Results: A total of 2759 patients underwent randomization. The incidence of high-risk diagnoses with complications in the first 30 d did not vary according to imaging method. The mean 6 mo cumulative radiation exposure was significantly lower in the U/S groups. Adverse events were similar across groups. Return ED visits, hospitalizations, and diagnostic accuracy did not differ significantly among the groups.
Conclusions: Initial ultrasonography was associated with lower cumulative radiation exposure than initial CT, without significant differences in high-risk diagnoses with complications, serious adverse events, pain scores, return ED visits, or hospitalizations.

Renal Nuclear Scan

Table 13. Renal Scan Tests

Type of Test	Uses	Radionuclide
Renogram	Assess renal function and collecting system: evaluation of renal failure, workup of urinary tract obstruction and renovascular HTN, investigation of renal transplant	IV^{99} mTc-pentetate (DTPA) or mertiatide (MAG3), and imaged at 1-3 s intervals with a γ-camera over the first 60 s to assess perfusion
Morphological	Assess renal anatomy: investigation of pyelonephritis and cortical scars	^{99m}Tc-DMSA ^{99m}Tc-glucoheptonate

Gynecological Imaging

Ultrasound
- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air-containing loops of bowel
  - indications: good initial investigation for suspected pelvic pathology
- TVUS provides a panoramic pelvic view and enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves due to reduced distances
  - indications: improved assessment of ovaries, first trimester development, and ectopic pregnancy

Hysterosalpingogram
- performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent
- indications: useful for assessing pathology of the uterine cavity and fallopian tubes, evaluating uterine abnormalities (e.g. bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)

CT/MRI
- indications: evaluating pelvic structures, especially those adjacent to the adnexa and uterus
- invaluable for staging gynecological malignancies and detecting recurrence

Sonohysterogram
- transcervical saline introduction into uterine cavity to provide enhanced endometrial visualization during TVUS examination
- indications: abnormal uterine bleeding, uterine cavity abnormalities that are suspected or noted on TVUS (e.g. leiomyomas, polyps, synechiae), congenital abnormalities of the uterine cavity, infertility, recurrent pregnancy loss
- contraindications: pregnancy, pelvic infection

Table 14. Typical and Atypical Findings on a Sonohysterogram

Finding	Typical	Atypical
Polyps	A well-defined, homogeneous, polypoid lesion isoechoic to the endometrium with preservation of the endometrial-myometrial interface	Cystic components, multiple polyps, broad base, hypoechogenicity, or heterogeneity
Leiomyoma	Well-defined, broad-based, hypoechoic, solid masses with shadowing. Overlying layer of endometrium is echogenic and distorts the endometrial-myometrial interface	Pedunculation or multilobulated surface
Hyperplasia and Cancer	Diffuse echogenic endometrial thickening without focal abnormality, although focal lesions can occur Endometrial cancer is typically a diffuse process, but early cases can be focal and appear as a polypoid mass	
Adhesions	Mobile, thin, echogenic bands that cut across the endometrial cavity	Thick, broad-based bands that can completely obliterate the endometrial cavity, as in Asherman's syndrome

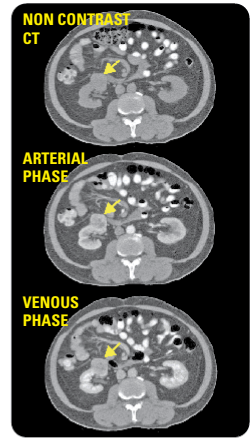


Figure 24. Triphasic CT of a renal cell carcinoma: showing arterial enhancing right renal lesion with venous washout (shunting)

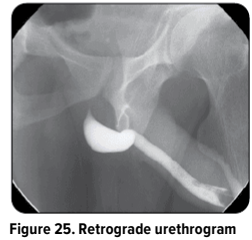


Figure 25. Retrograde urethrogram demonstrating stricture in the membranous urethra

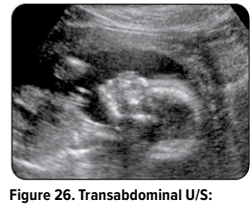


Figure 26. Transabdominal U/S: pregnancy, 18 wk fetus

Pregnancy should always be ruled out by β-hCG before CT of a female pelvis (or any organ system) is performed

Figure 27. Hysterosalpingogram: left hydrosalpinx

Adrenal Mass

- imaging modality: most often identified on CT scan as 'incidentaloma,' can also use CT/MRI to distinguish benign from malignant masses

Table 15. Adrenal Mass Findings on CT and MRI

Factors	Adrenocortical Adenoma	Adrenocortical Carcinoma	Pheochromocytoma	Metastasis
Diameter (CT)	Usually ≤3 cm	Usually ≥4 cm	Usually >3 cm	Variable around <3 cm
Shape (CT)	Smooth margins and round/oval	Irregular with unclear margins	Round/oval with clear margins	Oval/irregular with unclear margins
Texture (CT)	Homogeneous	Heterogeneous with mixed densities	Heterogeneous with cystic areas	Heterogeneous with mixed densities
Vascularity (CT)	Not highly vascular	Usually vascular	Usually vascular	Usually vascular
Washout of Contrast Medium on CT	≥50% at 10 min	<50% at 10 min	<50% at 10 min	<50% at 10 min
Growth	Stable or very slow (<1 cm/yr)	Usually rapid (>2 cm/yr)	Slow (0.5-1 cm/yr)	Variable
Other Findings	Usually low density due to intracellular fat	Necrosis, calcifications, and hemorrhage	Hemorrhage	Occasionally hemorrhage
MRI on T2 Weighted Imaging	Isointense in relation to liver	Hyperintense in relation to liver	Markedly hyperintense in relation to liver	Hyperintense in relation to liver

Neuroradiology

Skull Films

- rarely performed, generally not indicated for non-penetrating head trauma
- indications: screening for destructive bony lesions (e.g. metastases), metabolic disease, skull anomalies, postoperative changes and confirmation of hardware placement, skeletal surveys, multiple myeloma

CT

- CT is often the first line modality for most neuropathology, even in situations where MRI would lead to better characterization
- CT is frequently the initial study performed because of its speed, availability, and lower cost
  - acute craniofacial trauma: CT is best for visualizing "bone and blood;" use MRI when CT fails to detect an abnormality despite strong clinical suspicion
  - acute stroke: MRI ideal, CT most frequently used
  - acute headache with focal neurologic signs
  - suspected hemorrhage (epidural, subdural, subarachnoid, intraparenchymal)
  - suspected hydrocephalus
- vascular structures and areas of blood-brain barrier impairment are bright (e.g. hyperdense or enhancing) with contrast injection
- danger signs on head CT: space-occupying process, hemorrhage, edema, mass effect, midline shift, uncal and tonsillar herniation, loss of grey-white matter differentiation, hydrocephalus

Myelography

- introduction of water-soluble, low-osmotic contrast media into subarachnoid space via lumbar puncture followed by x-ray
- largely replaced by MRI or CT myelogram
- indications: excellent study for disc herniation, traumatic nerve root avulsion, patients with contraindication to MRI, extensive hardware from spinal surgery that may create MRI artifacts

MRI

- indications: finer neuroanatomic definition, better grey-white matter differentiation (especially T1-weighted series), better evaluation of edema extent (better tumour detection), allows evaluation of structures obscured by bony artifacts on CT (posterior fossa structures), multiplanar imaging helpful in preoperative assessment

Cerebral Angiography/CT Angiography/MR Angiography

- indications: evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissections
- conventional DSA remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (typically femoral) access and catheter manipulation, which confers risk of vessel injury (e.g. dissection, occlusion, vasospasm, emboli)
- MRA methods (phase contrast, time of flight, gadolinium-enhanced) and CTA are much less invasive without risk to intracranial or neck vessels
- MRA and CTA are often used first for the assessment of suspected TIA, subarachnoid hemorrhage, vasospasm, or aneurysms

Modality Based on Neuropathology Presentation

- Cognitive decline = CT
- Cord compression = MRI
- Decreased level of consciousness = CT
- Fish bone/other swallowed foreign body = CT
- Low back pain, radiculopathy = MRI
- Multiple sclerosis = MRI
- Neck infection = CT
- Orbital infection = CT
- Rule out bleed = CT
- Rule out aneurysm = CTA, MRA
- Seizure = CT
- Sinusitis = CT
- Stroke = CT, MRI
- Trauma = CT
- Weakness, systemically unwell = CT

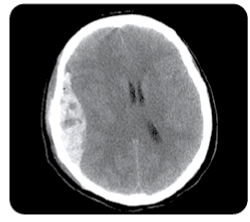


Figure 28. Epidural hematoma

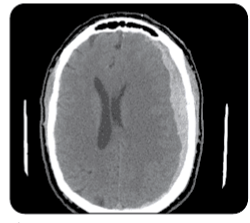


Figure 29. Subdural hematoma

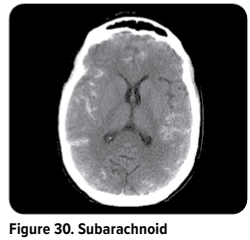


Figure 30. Subarachnoid hemorrhage

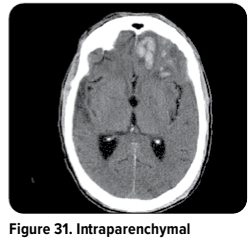


Figure 31. Intraparenchymal hemorrhage

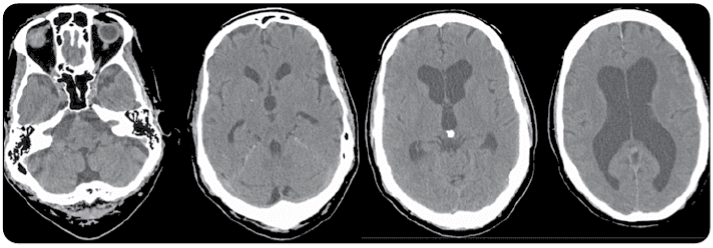


Figure 32. Hydrocephalus: ventricular dilatation (may see periventricular low attenuation due to transependymal CSF flow)

Table 16. Two Types of Hydrocephalus

Type	Cause
Communicating/Extraventricular	Impaired CSF reabsorption with unobstructed flow in ventricular system; imaging shows all ventricles dilated
Non-Communicating	Obstruction within the ventricular system (e.g. mass obstructing the aqueduct or foramen of Monro); imaging shows dilatation of ventricles proximal to the obstruction

Nuclear Medicine

- SPECT imaging using ^{99}mTc-exametazime (HMPAO) and ^{99}mTc-bicisate (ECD) assesses cerebral blood flow, as radionuclides diffuse rapidly across the blood-brain barrier and become trapped within neurons at a magnitude proportional to cerebral blood flow
- ^{18}FDG PET imaging assesses cerebral metabolic activity
- indications: differentiation of residual tumour vs. radiation necrosis; localization of epileptic seizure foci, and evaluation of atypical dementia

Approach to Head Computed Tomography

- think anatomically, work from superficial to deep
- scan: confirm the time and imaging of the correct patient, whether contrast was used, patient alignment, and presence of artifact
- skin/soft tissue: examine the soft tissue superficial to the skull for thickening suggestive of hematoma or edema; also evaluate the ear, orbital contents (globe, fat, muscles), parotid glands, muscles of mastication (masseter, temporalis, pterygoids), visualize pharynx
- bone and airspace (use the bone window): check calvarium, visualize mandible, visualize C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for fractures or opacity that may suggest fluid, pus, blood, or tumour; status of the orbital floor in cases of facial trauma (coronal series best)
- dura and subdural space: crescent-shaped hyperdensity in the subdural space suggests subdural hematoma; lentiform hyperdensity in the epidural space suggests epidural hematoma; check symmetry of dural thickness, where increased thickness may suggest the presence of blood
- parenchyma: asymmetry of the parenchyma suggests midline shift; poor contrast between grey and white matter suggests possible infarction, tumour, edema, infection, or contusion; a hyperdensity in the parenchyma suggests an enhancing lesions, intracerebral hemorrhage, or calcification; if central grey matter nuclei (e.g. globus pallidus, putamen, internal capsule) are not visible, suspect infarct, tumour, or infection
- ventricles/sulci/cisterns: examine position of ventricles for evidence of midline compression/shift; hyperdensities in the ventricles suggest ventricular/subdural hemorrhage; enlarged ventricles suggest hydrocephalus; obliteration of sulci may suggest presence of edema causing effacement, possible blood filling in the sulci, or tumour; cistern hyperdensities may suggest blood, pus, or tumour

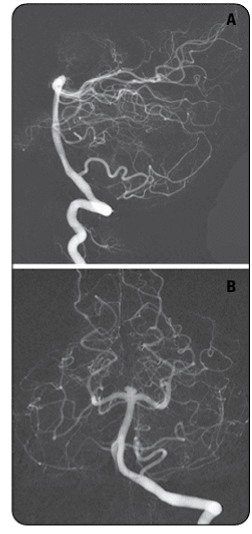


Figure 33. Sagittal (A) and coronal (B) views of the vertebrobasilar circulation (note the incidental basilar tip aneurysm)

Approach to the CT Head
Some = **S**can
Sore = **S**kin/**S**oft Tissue
Brains = **B**one/Airspace
Demonstrate = **D**ura/Subdural space
Pushed = **P**arenchyma
Ventricles = **V**entricles/Sulci/Cisterns

TIAs are not associated with radiological findings

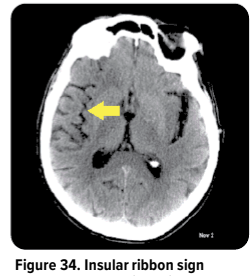


Figure 34. Insular ribbon sign (arrow): hypodensity of insular cortex representing early sign of infarction

Selected Pathology

- see Neurosurgery, NS4 for intracranial mass lesions
- see Neurosurgery, NS36 for head trauma and Plastic Surgery, PL31 for craniofacial injuries
- see Emergency Medicine, ER9 for spinal trauma
- see Neurosurgery, NS30 and Orthopedic Surgery, OR25 for degenerative spinal abnormalities

Cerebrovascular Disease (see Neurosurgery, NS22)

- pathogenesis of stroke: see Neurology, N51
- best imaging modality: MRI
- initial imaging modality: CT

Table 17. Temporal Findings of Infarction with CT and MRI

Time from Stroke Onset	CT	MRI
Hyperacute (0-24 h)	Usually normal within 6 h Edema (loss of grey-white matter differentiation – "insular ribbon sign," effacement of sulci, mass effect) Hyperattenuating artery "hyperdense MCA sign" representing intravascular thrombus/emboli may be seen in ischemic stroke Hyperattenuating acute blood surrounded by edema may be seen in hemorrhagic stroke	Hyperintensity on DWI within minutes of arterial occlusion due to restriction of water movement indicative of cytotoxic edema Hypointensity on ADC within minutes Hyperintensity on T2/FLAIR approximately 6 h after onset due to edema (loss of grey-white matter differentiation, effacement of sulci, mass effect)
Acute (24 h-1 wk)	Increasing edema (seen as hypoattenuation) may result in significant positive mass effect	Continued hyperintensity on DWI Hypointensity on ADC reaches nadir at 3-5 d and begins to increase Continued hyperintensity on T2/FLAIR
Subacute (1-3 wk)	Resolution of edema leads to increased attenuation of infarcted area that may regain near-normal density and mask stroke "fogging phenomenon"	Continued hyperintensity on DWI due to "T2 shine through" Intensity on ADC continues to rise, pseudo-normalizes at 10-15 d, and then surpasses that of surrounding normal tissue Continued hyperintensity on T2/FLAIR
Chronic (>3 wk)	Encephalomalacia (parenchymal volume loss) appears as hypoattenuation with negative mass effect	Hyperintensity on DWI/T2/FLAIR progressively decreases ADC intensity remains elevated

- carotid artery disease
  - best imaging modality: Duplex (Doppler U/S)
  - other modalities: MRA or CTA if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)

Multiple Sclerosis (see Neurology, N55)

- best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
- characteristic lesion locations: juxtacortical (grey-white junction), periventricular, infratentorial, and spinal cord
- cerebral lesions typical of MS:
  - involvement of the brainstem, cerebellum, and corpus callosum
  - "Dawson's fingers" refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  - plaques usually hyperintense on T2, and hypointense on T1
  - perivascular and interstitial edema may be prominent; enhances with gadolinium contrast when actively inflamed
- spinal cord lesions typical of MS:
  - little or no cord swelling
  - less likely to enhance with gadolinium contrast
  - incomplete involvement of the cord in cross-section (dorsolateral common)

CNS Infections

- **meningitis**
  - pathogenesis: inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via direct seeding of organisms through areas not protected by the blood-brain barrier (choroid plexus or circumventricular organs)
  - pathogens include: *S. pneumoniae, H. influenzae, N. meningitidis, L. monocytogenes*
  - best imaging modality: MRI (T2-weighted/FLAIR)
  - findings:
    - meningeal enhancement (following the gyri/sulci and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
  - a normal MRI does not rule out leptomeningitis
- **herpes simplex encephalitis** (see Infectious Diseases, ID18)
  - pathogenesis: inflammation of the brain parenchyma secondary to infection with herpes simplex virus, asymmetrically affects the limbic regions of the brain (i.e. temporal lobes, orbitofrontal region, insula, and cingulate gyrus)
  - best imaging modality: MRI (T1- and T2-weighted)

DDx for Ring Enhancing Cerebral Lesion

MAGIC DR
Metastasis
Abscess
Glioblastoma multiforme
Infarction (subacute/chronic)
Contusion/hematoma
Demyelinating disease (e.g. MS)
Radiation necrosis

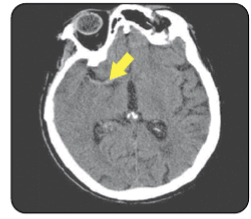


Figure 35. CT image of early infarct: hyperdense artery

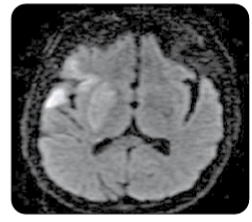


Figure 36. DWI of patient with right frontotemporal infarct

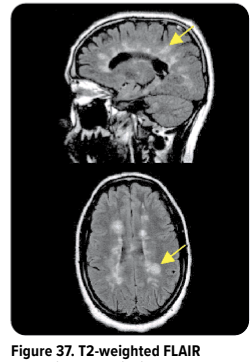


Figure 37. T2-weighted FLAIR (A) sagittal (B) axial images of multiple sclerosis with periventricular "Dawson's Fingers"

- findings:
  - acute (within 4-5 d): asymmetric high intensity lesions on T2 MRI in temporal and inferior frontal lobes strongly suggestive
  - CT may show hypodensity in temporal lobe and insula; rarely basal ganglia involvement
  - long-term may show parenchymal loss to affected areas
- DDx: infarct, tumour, status epilepticus, limbic encephalitis

- **cerebritis/cerebral abscess**
  - pathogenesis: an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms, commonly located in the distribution of the MCA
  - pathogens include: *S. aureus* (often in IV drug users, nosocomial), *Streptococcus*, Gram negative bacteria, *Bacteroides*
  - best imaging modality: MRI including DWI imaging series (abscess will be DWI positive); CT still used as a viable alternative
  - findings according to one of four stages of abscess formation:
    - early cerebritis (1-3 d): inflammatory infiltrate with necrotic centre, low intensity on T1, high intensity on T2
    - late cerebritis (4-9 d): ring enhancement may be present
    - early capsule (10-13 d): ring enhancement
    - late capsule (>14 d): well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperintensity on T2

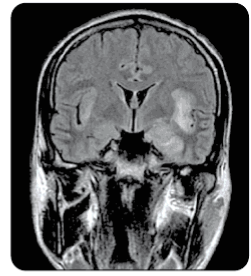


Figure 38. T2-weighted (FLAIR) coronal image of herpes simplex virus encephalitis affecting temporal lobes

Musculoskeletal System

Modalities

- see *Imaging Modalities*, MI2 for advantages and disadvantages of the following:

Plain Film/X-Ray
- usually initial study used in evaluation of bone and joint disorders
- indications: fractures and dislocations, arthritis, assessment of malunion or nonunion, orthopedic hardware, and bone lesions (initial)
- minimum of two orthogonal views (usually AP and lateral) to rule out a fracture/assess bone lesion
- image the joint proximal and distal to injury site to ensure there is no associated dislocation or second fracture site, particularly important with bony rings (e.g. radius/ulna, tibia/fibula)
- soft tissue assessment limited, but can identify joint effusions (elbow, knee), soft tissue gas (necrotizing fasciitis), and radiodense foreign bodies

CT
- evaluation of fine bony detail
- indications: preoperative assessment of complex, comminuted, intra-articular, or detection of radiographically-occult fractures including scaphoid, skull, spine, pelvis, midfoot, and calcaneus
- evaluation of soft tissue calcification/ossification and bone tumours

MRI
- indications: evaluation of internal derangement of joints (e.g. ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses, infection of bone (osteomyelitis), occult fracture assessment

Ultrasound
- indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection and characterization of soft tissue masses (i.e. cystic or solid), detection of foreign bodies, U/S-guided biopsy and injections, bone/joint evaluation pre-ossification (e.g. DDH in early months), dynamic imaging (i.e. snapping hip, extensor carpi ulnaris subluxation), small joint Doppler assessment for arthritis
- Doppler determines vascularity of structures

Nuclear Medicine (Primarily Bone Scan/Skeletal Scintigraphy)
- determines the location and extent of bony lesions using radiopharmaceuticals (^{99}mTc-methylene diphosphonate)
- increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
- indications: bone lesion characterization, occult fractures (spine, scaphoid, small bones), bone pain of unknown origin, staging or restaging of cancer with bony metastases (or primary bone cancer), imaging of polyarthritis, imaging of arthroplasty complications like loosening or infection, osteomyelitis imaging
  - when used to assess for osteomyelitis, usually done in combination with gallium or white blood cell scan
- DDx of positive bone scan: bone metastases (primary breast, prostate, lung, thyroid), primary bone tumour, arthritis, fracture, infection, anemia, Paget's disease
- caution: bone tumours that do not elicit osteoblastic response are often occult on bone scan (myeloma, highly vascular tumours such as RCC, or thyroid carcinoma)

Characterization of Rotator Cuff Tears: Ultrasound vs. Magnetic Resonance Imaging
Orthopedics 2017;40:e124-e130
Purpose: Determine whether U/S or MRI is more accurate and precise in evaluating the characteristics of full-thickness rotator cuff tears in a surgical population.
Methods: Review of 114 patients who underwent repair of a full-thickness rotator cuff tear over a 1 yr period. Of these patients, 61 had both preoperative MRI and U/S for review. Three radiologists evaluated each U/S and MRI in a randomized, blinded fashion on 2 occasions. Tear size, retraction status, muscle atrophy, and fatty infiltration were analyzed and compared between the 2 modalities.
Results: U/S measurements were statistically smaller in both tear size (P=0.001) and retraction status (P=0.001) compared with MRI. MRI showed greater interobserver reliability in assessment of tear size, retraction status, and atrophy.
Conclusion: Independent observers are more likely to agree on measurements of the characteristics of rotator cuff tears when using MRI compared with U/S. As tear size increases, the 2 image modalities show greater differences in measurement of tear size and retraction status. U/S may be best used to identify a tear, and MRI is superior for use in surgical planning for larger tears.

Approach to Bone X-Rays

- identification: name, MRN, age of patient, type of study, region of investigation
- soft tissues: swelling, calcification/ossification
- joints: alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, symmetry of affected joint
- bone: periosteum, cortex, medulla, trabeculae, density, articular surfaces, bone destruction, bone production, appearance of the edges or borders of any lesions

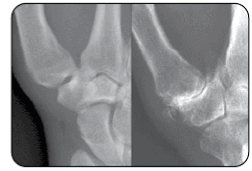


Figure 39. X-ray findings of first carpometacarpal joint: normal image (left) and osteoarthritis (right) with joint space narrowing and subchondral sclerosis

Trauma

Fracture/Dislocation

- description of fractures
- site of fracture (bone, region of bone, intra-articular vs. extra-articular)
- pattern of fracture line (simple vs. comminuted)
- displacement (distal fragment with reference to the proximal fragment)
- soft tissue involvement (calcification, gas, foreign bodies)
- type of fracture (stress vs. pathologic)
- for specific fracture descriptions and characteristics, see Orthopedic Surgery, OR5

Arthritis

- see Rheumatology for radiographic features of specific arthritides

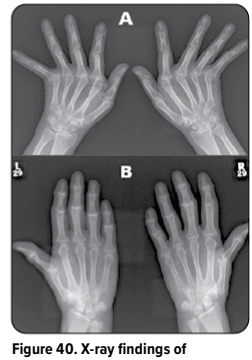


Figure 40. X-ray findings of rheumatoid arthritis (A) compared with osteoarthritis (B)

Bone and Soft Tissue Tumours

Bone Tumours

- benign bone lesions (e.g. hemangiomas, enostoses, enchondromas) are more common than malignant bone lesions
- primary bone tumours are rare after 3rd decade; metastases to bone are relatively common after 3rd decade
- MRI is helpful for detection, characterization, staging, soft tissue involvement, and surgical planning
- plain film is important for assessing pattern of destruction, mineralization, and aggressiveness
- biopsy may be required if no primary is identified, or suspect primary bone tumour
- may present with pathological fractures or bone pain
- most common metastatic bone tumours: breast, prostate, lung
- for specific bone tumours, see Orthopedic Surgery, OR50

Soft tissue Tumours

- soft tissue masses are most commonly benign
- common benign soft tissue masses include lipomas, benign peripheral nerve sheath tumours, and vascular malformations
- soft tissue sarcomas are uncommon but require urgent workup and specialized treatment
- U/S is helpful for differentiating lipoma from cyst from mass
- MRI is helpful for diagnostic workup
- if the mass is not clearly benign, biopsy or wide excision is required for diagnosis

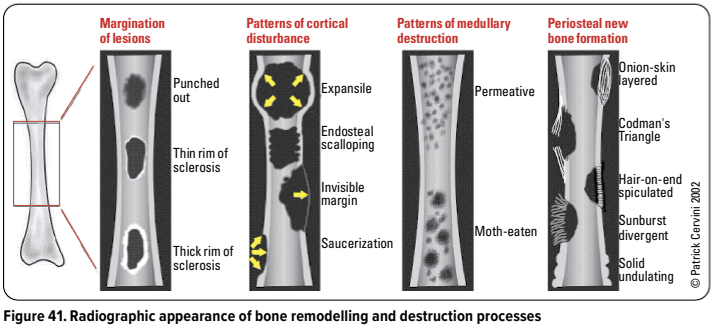


Figure 41. Radiographic appearance of bone remodelling and destruction processes

Lytic = decreased density
Sclerotic = increased density

Table 18. Distinguishing Benign from Malignant Bone Lesions on X-Ray

Benign	Malignant
No periosteal reaction or benign appearing reaction (e.g. uniform smooth periosteal thickening as seen in a healing fracture)	Acute periosteal reaction • Codman's triangle • "Onion skin" • "Sunburst"
Sharp, well-demarcated borders, narrow zone of transition (between lesion and normal bone, suggesting slow-growing lesion)	Poorly defined borders, with a wide zone of transition, or infiltrative (suggesting fast-growing lesion)
Well-developed bone formation	Varied bone formation
Intraosseous and even calcification	Extraosseous and irregular calcification
No soft tissue mass	Soft tissue mass present
No cortical destruction or uniform cortical destruction in some low grade and locally aggressive benign lesions	Aggressive cortical destruction or tumour infiltration without cortical destruction

Adapted from: Buckholtz RW, Heckman JD. Rockwood and Green's Fractures in Adults. Vol. 1. Philadelphia: Lippincott Williams & Wilkins, 2001. 558 p

Infection

Osteomyelitis

- modern workup includes MRI or x-ray
  - x-ray can detect osseous destruction seen with subacute osteomyelitis (>1 wk) or chronic change, and can detect lucencies surrounding infected orthopedic hardware
  - MRI is more sensitive, with loss of normal fatty T1 marrow signal diagnostic of esteomyelitis, and can also assess for extra-osseous soft tissue involvement or spread
- nuclear medicine (^{99}mTc, followed by ^{111}In-labeled white cell scan or gallium radioisotope scan) may be used where available, or in the setting of hardware

Septic Arthritis

- surgical emergency in large joints (i.e. hip)
- x-ray usually normal early
- aspiration required if concern for septic arthritis
- imaging modalities can detect joint fluid in some points, but imaging cannot rule out septic arthritis

Necrotizing Fasciitis

- surgical emergency
- X-ray can detect gas, but absence does not rule out necrotizing fasciitis
- in the perineum, referred to as Fournier's gangrene
- surgical referral required

Metabolic Bone Disease

Osteoporosis

- reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
  - typical sites of fragility fracture: spine, hip, pelvis, wrist, humerus, rib
- DEXA: gold standard for measuring bone mineral density, typically measured hip and lumbar spine
- Canadian Association of Radiologist and Osteoporosis Canada (CAROC) guidelines for use of DEXA: diagnosis, determining fracture risk/therapy, and monitoring
  - diagnosis driven by T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - osteopenia: −2.5< T-score <−1
    - osteoporosis: T-score ≤-2.5
  - Z-score: the number of standard deviations from the age-matched mean, helpful in diagnosing secondary osteoporosis
  - risk of fracture: patients classified as low, medium, or high risk based on bone mineral density, age, history of previous fragility fractures, and steroid therapy. Presence of certain criteria such as hip or spine fragility fracture automatically places patients in the high risk category
- see Endocrinology, E46

Hyperparathyroidism

- most common cause is renal failure (secondary hyperparathyroidism)
- chondrocalcinosis is a common complication
- calcium crystal deposition in hyaline cartilage or fibrocartilage (including arteries and periarticular soft tissue)
- resorption of bone typically in hands (subperiosteal and at tufts), sacroiliac joints (subchondral), skull ("salt and pepper" appearance), subligamentous resorption (ischial tuberosity, trochanters, and clavicle), osteoclastoma (brown tumours)
- "rugger jersey spine": band-like osteosclerosis at superior/inferior margins of vertebral bodies

Paget's Disease
- abnormal remodelling involving single or multiple bones – especially skull, spine, pelvis
- 3 phases: 1st phase = lytic, 2nd phase = mixed (lytic/sclerotic), 3rd phase = sclerotic
- coarsening of the trabeculae with bone expansion
- bone softening/bowing
- bone scintigraphy will reveal high activity
- thickened cortex; widening of diploe in skull, osteoporosis circumscripta (lytic phase in skull); "blade of grass" sign (lytic phase in a long bone like the femur); "picture frame" appearance to vertebra (due to thickening and sclerosis of vertebral cortex)
- see Endocrinology, E50

Nuclear Medicine

Brain

- ^{99}mTc-exametazime (HMPAO) and ^{99}mTc-bicisate (ECD) imaging used in SPECT to assess cerebral blood flow and cellular metabolism
  - taken up predominantly in grey matter
  - used for dementia, traumatic brain injury; and to a lesser extent vasculitis, neuropsychiatric disorders, and occasionally stroke
- PET imaging to assesses metabolic activity
  - used for dementia imaging, grading and staging of brain tumours, occasionally for seizure disorder imaging, and vasculitis
- CSF imaging via intrathecal administration of ^{111}In DTPA
  - to evaluate CSF leak or to differentiate normal pressure hydrocephalus from brain atrophy
- CSF shunt evaluation for obstruction (most commonly ventriculoperitoneal) with sterile or pyrogen free ^{99}mTc (usually) or ^{111}In-DTPA

Thyroid

Radioactive Iodine Uptake (see Endocrinology, E27)
- index of thyroid function (trapping and organification of iodine)
- radioactive ^{123}I given PO to fasting patient (small quantity) and percentage of administered iodine taken up by thyroid is measured
- increased RAIU: toxic multinodular goitre, toxic adenoma, Graves' disease
- decreased RAIU: subacute thyroiditis, late Hashimoto's disease, exogenous thyroid hormone or iodine, falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed, taking supplements containing desiccated thyroid)
- important – iodine uptake helps in the differential of hyperthyroidism only, not hypothyroidism

Thyroid Imaging (Scintiscan)
- ^{99}mTc-pertechnetate IV or radioactive iodine (^{123}I)
- provides functional anatomic detail
- hot (hyperfunctioning) lesions: usually benign (e.g. adenoma, toxic multinodular goitre), cancer unlikely (<1%) – No FNA
- cold (hypofunctioning) lesions: cancer must be considered until biopsy negative even though only 6-10% are cancerous – decision to biopsy should be based on clinical and sonographic features
- isointense (i.e. "warm" lesions): cancer must be considered as an isointense lesion; may represent cold nodules superimposed on normal tissue; if cyst suspected, correlate with U/S

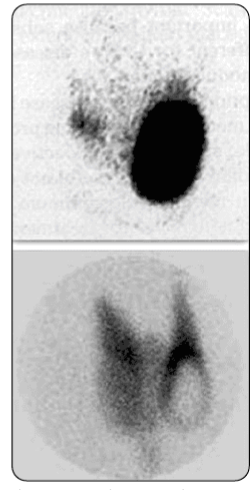


Figure 42. Multinodular goitre (top). Cold nodule (bottom)

Radioiodine Ablation
- ^{131}I for Graves' disease, multinodular goitre, thyroid cancer (in the case of thyroid cancer, ablation performed at higher dose and after thyroidectomy)
- serum thyroglobulin used to detect recurrent thyroid cancer in a patient who has received ablation
- advice should be given for patient-specific precautions to remain away from family members and caregivers to reduce radiation exposure after thyroid ablation, do not initiate pregnancy for 6 mo, small risk of exophthalmos, thyroid storm, secondary malignancy

Respiratory

V/Q Scan
- evaluate areas of lung in which there is a ventilation/perfusion mismatch
- ventilation scan – assess air flow within lungs
  - patient breathes radioactive gas (nebulized ^{99}mTc-DTPA, ^{133}Xe, or most commonly Technegas™) through a closed system, filling alveoli proportionally to ventilation
  - ventilation scan defects indicate: airway obstruction (i.e. air trapping), chronic lung disease, bronchospasm, tumour mass obstruction

- perfusion scan – assess blood circulation within lungs
  - radiotracer injected IV (^{99}mTc-MAA) → trapped in pulmonary capillaries (0.1% of arterioles occluded) according to blood flow
  - relatively contraindicated in severe pulmonary HTN, right-to-left shunt, previous history of pneumonectomy, and small children
- indicated to rule out PE
  - areas of lung that are well-ventilated but not perfused (unmatched defect) are suspicious for acute infarction
  - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
  - useful in finding clinically important emboli
- modified V/Q scan (perfusion only, lower dose contrast) may be used for pregnant patients if CXR is normal or if there are ventilatory problems

Cardiac

Myocardial Perfusion Scan/Nuclear Stress Test

- indications: diagnose and assess treatment of coronary artery disease (CAD), preoperative risk stratification, viability testing before percutaneous intervention or bypass surgery
- ^{99}mTc-sestamibi or ^{99}mTc-tetrofosmin is injected: at peak exercise (85% max predicted heart rate by the Bruce protocol, chest pain, ECG changes), after persantine challenge (vasodilator), or after dobutamine infusion (chronotropic, again to 85% predicted heart rate)
- persistent defect (present at rest and stress) suggests infarction or myocardial scar
- reversible defect (only present during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- COURAGE trial indicates that patients with >10% ischemic myocardium benefit most from revascularization
- see Cardiology and Cardiac Surgery, C16

Radionuclide Ventriculography

- ^{99}mTc-tagged to red blood cells
- non-invasive method of assessing ventricular function and intracardiac hemodynamics (i.e. ejection fraction, presence of shunts, ventricular volume, and regional wall motion)
- cardiac MUGA scan sums multiple cardiac cycles, usually at least 200 beats
- indications: most commonly to monitor potential cardiac toxicity with chemotherapy or herceptin, as a gold standard of ejection fraction in defibrillator workup

Abdomen and Genitourinary System

HIDA Scan (Cholescintigraphy)

- IV injection of ^{99}mTc-disofenin (DISIDA) or ^{99}mTc-mebrofenin which is bound to protein, taken up by hepatocytes, and excreted into the biliary system
- indicated for patients who are suspected of having an obstruction in the biliary tract, to assess for bile leaks postoperatively, and for biliary dyskinesia
- indicated in workup of cholecystitis when abdominal U/S result is equivocal:
  - acute cholecystitis: no visualization of gallbladder at 4 h or 1 h after administration of morphine
  - chronic cholecystitis: no visualization of gallbladder at 1 h but seen at 4 h or after morphine administration
- DDx of obstructed cystic duct: acute/chronic cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting <4 h or >24 h

RBC Scan

- IV injection of radiotracer with sequential images of the abdomen (^{99} mTc RBCs)
- GI bleed evaluation
  - if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed
  - if bleeding acutely at >0.5 mL/min, use angiography (more specific, better for localizing, both diagnostic and therapeutic)
- liver lesion evaluation
  - hemangioma has characteristic appearance: cold early (limited blood flow to lesion), fills in later (accumulation of tagged cells greater than surrounding liver parenchyma)

Urea Breath Test

- indication: diagnosis of gastric *H. pylori* infection
- patient administered ^{14}C-labelled urea orally, urea metabolized by *H. pylori* to ammonia and $^{14}CO_2$, ^{14}C-labelled CO_2 is measured via plastic filament detectors or liquid scintillation

Functional Renal Imaging
- evaluation of renal function and anatomy using ^{99}mTc DTPA (static imaging) or ^{99}mTc MAG3 (dynamic imaging)
- frequently used to provide index of relative function between two kidneys
- in adults, used to assess for UPJ obstruction, renal transplants, or as a nuclear glomerular filtration rate study in patients wanting to donate kidneys
- in children, used to assess for pyelonephritis and reflux

Interventional Radiology

Vascular Procedures

Angiography
- injection of contrast material through a catheter placed directly into an artery or vein to delineate vascular anatomy
- can be used in the operating room to provide fluoroscopic guidance for exposure of diseased vessel
- indications: diagnosis of primary occlusive or stenotic vascular disease, aneurysms; coronary, carotid and cerebral vascular disease; PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (endovascular aneurysm repair, thrombolysis, stenting, and angioplasties)
- complications (<5% of patients): puncture site hematoma, pseudoaneurysm, dissection, thrombosis, infection, AV fistula, embolic occlusion of a distal vessel
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (colour Doppler U/S, CTA, and MRA)
- see *Neuroradiology*, MI19

Percutaneous Transluminal Angioplasty and Stents
- introduction and inflation of a balloon into a stenosed or occluded vessel to restore distal blood supply
- common alternative to surgical bypass grafting with 5 yr patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary, and carotid artery stenoses are amenable to treatment
- vascular stents may help improve long-term results by keeping the vessel wall patent after angioplasty; also used for angioplasty failure or complications
- stent grafts (metal mesh covered with durable fabric) may provide an alternative treatment option for aneurysms and AV fistulas
- complications: similar to angiography, but also includes vessel rupture

Thrombolytic Therapy
- may be systemic (IV) or catheter directed
- infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
- can restore blood flow in a vessel obstructed with a thrombus or embolus
- indications: treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of deep venous thrombosis (DVT) or PE
- complications: bleeding, stroke, distal embolus, reperfusion injury in delayed intervention with myoglobinuria, and renal failure if advanced ischemia present

Embolization
- injection of occluding material into vessels
- permanent agents: amplatzer plugs, coils, glue, and onyx
- temporary: gel foam, autologous blood clots
- indications: management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of arteriovenous malformation, preoperative treatment of vascular tumours (bone metastases, renal cell carcinoma), ovarian vein embolization for chronic pelvic pain (pelvic venous disease), varicocele embolization for infertility, symptomatic uterine fibroids
- complications: post-embolization syndrome (pain, fever, leukocytosis), unintentional embolization of a non-target organ with resultant ischemia

Inferior Vena Cava Filter
- insertion of temporary or permanent metallic "umbrellas" to mechanically trap DVT emboli to prevent subsequent PE
- inserted via femoral vein, jugular vein, or basilic vein
- usually placed infrarenally to avoid renal vein thrombosis
- indications: contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation therapy necessitating termination of anticoagulation (e.g. life-threatening hemorrhage)

Thrombolytic Therapy for Pulmonary Embolism
Cochrane DB Syst Rev 2015;9:CD004437
Purpose: To assess the effects of thrombolytic therapy in patients with acute pulmonary embolism (PE).
Methods: Systematic review of RCTs evaluating thrombolytic therapy followed by heparin vs. heparin alone, heparin plus placebo or surgical intervention in patients with acute PE. Main outcomes of interest were death, recurrence of PE, and major and minor hemorrhagic events.
Results: Twenty-one trials (n=2401) were included. Thrombolytics plus heparin was associated with a reduction in odds of death relative to heparin alone or heparin plus placebo (OR 0.58; 95% CI, 0.38 to 0.88, low-certainty) and recurrence of PE (OR 0.54; 95% CI, 0.32 to 0.91, low-certainty). Incidence of major hemorrhagic events was higher in the thrombolytic group as compared to control (OR 2.84; 95% CI, 1.92 to 4.20), as well as minor hemorrhagic events (OR 2.97; 95% CI, 1.66 to 5.30). Length of hospital stay was reduced in the thrombolytics group as compared to controls (mean difference (MD) −1.40 days; 95% CI, −2.69 to −0.11).
Conclusion: Low-certainty evidence suggests thrombolytics reduce death following acute PE compared with heparin and may be helpful in reducing PE recurrence, but may cause more hemorrhagic events.

Central Venous Access
- variety of devices available (PICC, external tunneled catheter (Hickman or dialysis catheters), subcutaneous port (Portacath®))
- indications: chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
- complications: venous thrombosis, central venous stenosis, infection including sepsis, and pneumothorax

Breast Imaging

Modalities

Mammography

Description
- x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities (see General and Thoracic Surgery, GS67)
- routine evaluation involves two standard views: cranio-caudal and medial-lateral-oblique

Indications
- screening (for guidelines, see Family Medicine, FM4)
  - guidelines may vary by region
- surveillance
  - follow-up of women with previous breast cancer
- diagnostic: includes mammography with special views and/or U/S
  - workup of an abnormality that may be suggestive of breast cancer including a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, overlying skin changes, and spontaneous serous or sanguinous nipple discharge from a single duct
  - women with abnormal screening mammograms
  - suspected complications of breast implants

Table 19. Breast Imaging Reporting and Data System (BI-RADS®) Mammography Categories

Assessment Categories	Imaging Findings	Likelihood of Malignancy (%)	Follow-Up Recommendations
BI-RADS 0	Incomplete	N/A	Additional imaging Comparison to prior films
BI-RADS 1	Negative	~0	Routine screening
BI-RADS 2	Benign	~0	Routine screening
BI-RADS 3	Probably benign Likelihood of malignancy is <2%	0-2	Unilateral mammogram at 6 mo
BI-RADS 4	Suspicious abnormality	3-94	Biopsy
BI-RADS 4A	Low suspicion for malignancy	3-10	Biopsy
BI-RADS 4B	Low suspicion for malignancy	11-50	Biopsy
BI-RADS 4C	Low suspicion for malignancy	51-94	Biopsy
BI-RADS 5	Highly suspicious of malignancy	≥95	Biopsy
BI-RADS 6	Malignancy confirmed by biopsy	100	Definitive therapy

Breast Ultrasound

Indications
- characterization of palpable abnormalities
  - U/S is 1st line in <30 yr – denser breast tissue makes mammograms less sensitive in young females
  - first line in lactating and pregnant women
  - >30 yr need mammogram first
- further characterization of mammographic findings
- guidance for interventional procedures

Breast MRI

Description
- contrast-enhanced MRI of the breasts
- sensitive for detecting invasive breast cancer (95-100%) but specificity variable (37-97%)
- for diagnosis, used only after mammography and U/S investigation
- use as a screening modality is limited to high-risk patients, in conjunction with mammography

Indications
- "problem-solving" of indeterminate findings following complete mammographic and U/S workup
- evaluation of occult primary in patients presenting with axillary metastases
- evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
- evaluation of previously diagnosed breast cancer: positive margins, recurrence, response to chemotherapy
- high-risk screening
  - known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer, or untested first-degree relative of a carrier of such a gene mutation
  - family history consistent with a hereditary breast cancer syndrome and/or estimated personal lifetime cancer risk >25%
  - high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ)
  - radiation therapy to chest (before age 30)

Breast Interventional Procedures

Description
- includes core needle biopsy, stereotactic biopsy, MRI-guided biopsy, abscess drainage, and cyst aspiration

Indications
- cystic mass: complex cyst, symptomatic, suspected abscess
- solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5)
- suspicious calcifications: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) – stereotactic biopsy
- initial percutaneous biopsy procedure that was insufficient or discordant with imaging
- presurgical wire localization of a lesion

Breast Findings

Breast Masses
- definition: a space-occupying lesion seen in two different projections; if seen in only a single projection it should be called an "asymmetry" until its three-dimensionality is confirmed

Table 20. Mammographic Features of Benign and Malignant Breast Masses

	Benign	Malignant
Shape	Oval, round, lobular	Irregular
Margin	Circumscribed, well-defined	Indistinct, microlobulated, spiculated
Density	Radiolucent (oil cyst, lipoma, fibrolipoma, galactocele, hamartoma)	Radiodense
Calcifications (± mass)	Popcorn (hyalinizing fibroadenoma), lucent centred (oil cyst/fat necrosis), layering (milk of calcium), vascular, round, scattered	Pleomorphic (vary in size and shape), amorphous (indistinct), fine linear, coarse heterogeneous, regional, segmental, clustered

Other Findings
- tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
- intramammary lymph node: typical lymph nodes are well-circumscribed, reniform and often have a fatty notch and centre; usually <1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty centre or notch) are well seen, the lesion is almost always benign and insignificant
- focal asymmetry: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
- if focal compression shows mass-like character – or if the area can be palpated – biopsy generally recommended

Landmark Radiology Trials

Trial Name	Reference	Clinical Trial Details
VASCULAR PROCEDURES		
PREPIC	NEJM 1998;338:409-416	**Purpose**: To study the efficacy and safety of vena caval filters in preventing the formation of PEs in patients with proximal DVT. **Methods**: RCT consisting of 400 patients with proximal DVT who were randomized to receive heparin in conjunction with either a caval filter or no filter. **Results**: 2 patients within the treatment group and 9 patients within the control group had experienced a PE within 12 d. 37 patients within the treatment group and 21 patients within the control group experienced recurrent DVT within 2 yr. **Conclusion**: Benefits of vena caval filters were counterbalanced by their risks. Filters resulted in no significant difference in mortality or other outcomes and although they prevented PE within 12 d, they increased the risk of recurrent DVT within 2 yr.
EVAR	NEJM 2010;362:1863-1871	**Purpose**: To understand the long term implications of endovascular repair of abdominal aortic aneurysms. **Methods**: RCT consisting of 1252 patients with abdominal aortic aneurysms were randomized to undergo an endovascular or open repair. The outcomes of interest included mortality, graft-related complications, and re-interventions. **Results**: The 30 d postoperative mortality was lower in the endovascular repair group (1.8% vs. 4.3%). However, due to graft ruptures, the mortality rates equilibrated over time. The rates of graft-related complications and re-interventions were higher in the group that underwent endovascular repair. **Conclusion**: Mortality at 30 d post-operation was significantly lower for endovascular repair compared to open repair. At the end of follow-up (5-10 yr), there was no significant difference in mortality and rates of complication were higher in the endovascular treatment group.
NCT03702413	NEJM 2022; 386:1303-1313	**Title**: Endovascular Therapy for Acute Stroke with a Large Ischemic Region **Purpose**: Endovascular therapy is often avoided for patients with large cerebrovascular infarctions, however the benefits of endovascular therapy in combination with stroke medical care has not been studied. **Methods**: RCT consisting of 203 patients with occlusion of large cerebral vessels and an Alberta Stroke Program Early Computed Tomographic Score between 3-5. Patients were randomized to receive endovascular therapy in conjunction with medical care or medical care alone. The primary outcome is a modified Rankin score between 0 and 3, 90-d post-treatment. **Results**: A larger proportion of patients treated with endovascular therapy in conjunction with medical care achieved a modified Rankin score between 0 and 3 (31%) compared to medical care alone (12.7%). **Conclusion**: In patients with large cerebrovascular occlusions, treatment with endovascular therapy in conjunction with medical care resulted in improved functional outcomes when compared to treatment with medical care alone.
AMACING	Lancet 2017;389:1312-1322	**Title**: Prophylactic Hydration To Protect Renal Function From Intravascular Iodinated Contrast Material In Patients At High Risk Of Contrast-Induced Nephropathy **Purpose**: To determine the effectiveness of prophylactic hydration in protecting renal function in high risk individuals. **Methods**: RCT of 660 patients at high risk of contrast-induced nephropathy (eGFR 30-59) who were receiving iodinated contrast for an elective procedure. Patients were randomized to receive IV 0.9% NaCl vs. no treatment. Primary outcome was contrast-induced nephropathy (over 35% or 44µmol increase in serum creatinine from baseline in 2-6 days). **Results**: Contrast-induced nephropathy was observed in 2.7% of patients receiving prophylactic hydration and in 2.6% of non-hydrated patients. **Conclusion**: No prophylactic hydration is non-inferior to IV hydration in the prevention of contrast-induced nephropathy in high-risk patients.
RENOVATE-COMPLEX-PCI	NEJM 2023;388:1668-1679	**Title**: Intravascular Imaging-Guided or Angiography-Guided Complex PCI **Purpose**: To assess the clinical outcomes in patients receiving intravascular imaging-guided percutaneous coronary intervention (PCI) as compared to angiography-guided PCI in patients with complex coronary-artery lesions. **Methods**: RCT of 1639 patients with complex coronary-artery lesions who were randomized to undergo either intravascular imaging-guided PCI or angiography-guided PCI. Primary endpoint was death from cardiac causes, target-vessel-related MI, or target-vessel revascularization. **Results**: Cardiac-related death occurred in 1.7% and 3.8% of patients in the intravascular imaging-guided PCI and angiography-guided PCI groups, respectively. Target-vessel-related MI occurred in 3.7% and 5.6% of patients, respectively, and target-vessel revascularization occurred in 3.4% and 5.5% of patients, respectively. **Conclusion**: As compared to angiography-guided PCI, intravascular imaging-guided PCI is associated with lower risk of death from cardiac causes, target-vessel-related MI, or target-vessel revascularization.
DISCHARGE	NEJM 2022;386:1591-1602	**Title**: CT or Invasive Coronary Angiography in Stable Chest Pain **Purpose**: To assess the rates of major adverse cardiovascular events between CT and invasive coronary angiography (ICA) in the diagnosis of obstructive CAD. **Methods**: RCT of 3561 patients with stable chest pain and an indeterminate pretest probability of obstructive CAD who were randomized to receive CT or ICA as initial diagnostic testing. Primary outcome was a major adverse CV event in a 3.5 yr period. Secondary outcomes were complications of the procedure and angina pectoris. **Results**: Major adverse CV events were observed in 2.1% and 3.0% of patients in CT and ICA groups, respectively (HR 0.7; 95% CI, 0.46-1.07; P=0.10). Major procedure-related complications were observed in 0.5% and 1.9% of patients in CT and ICA groups, respectively (HR 0.26; 95% CI, 0.13-0.55). Angina was reported in 8.8% and 7.5% of patients, respectively (OR 1.17; 95% CI, 0.92-1.48). **Conclusion**: The risk of major adverse cardiovascular events was comparable between CT and ICA groups. CT was associated with a lower risk of major procedure-related complications.
NUCLEAR MEDICINE		
ESTIMABL2	NEJM 2022; 386:923-932	**Title**: Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer **Purpose**: To assess the clinical benefit of postoperative radioiodine, after thyroidectomy in low-risk thyroid cancer. **Methods**: RCT consisting of 730 patients with low-risk differentiated thyroid cancer undergoing thyroidectomy. Patients were randomized to either receive or not receive radioiodine. The outcomes of interest were the presence of abnormal radioiodine foci, abnormal neck ultrasound, or presence of increased thyroglobulin/thyroglobulin antibodies. **Results**: There was no significant difference in postoperative abnormalities between patients that received (4.1%) and did not receive postoperative radioiodine (4.4%). **Conclusion**: The use of radioiodine is negligible in the prevention of post-thyroidectomy abnormalities.

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NP Nephrology

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Acronyms

ACEI	angiotensin converting enzyme inhibitor	DIC	disseminated intravascular coagulation	NS	normal saline
ACR	urine albumin to creatinine ratio	DKA	diabetic ketoacidosis	p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
ADH	antidiuretic hormone	DM	diabetes mellitus	PCT	proximal convoluted tubule
AG	anion gap	ECF	extracellular fluid	PJP	*Pneumocystis jiroveci* pneumonia
AIN	acute interstitial nephritis	eGFR	estimated glomerular filtration rate	PKD	polycystic kidney disease
AKI	acute kidney injury	ESR	erythrocyte sedimentation rate	PTH	parathyroid hormone
ANA	antinuclear antibody	ESRD	end-stage renal disease	R&M	routine and microscopy
ARB	angiotensin receptor blocker	FENa	fractional excretion of sodium	RAAS	renin-angiotensin-aldosterone system
ASA	acetylsalicylic acid	FF	filtration fraction	RBF	renal blood flow
ASOT	anti streptolysin-O titer	FSGS	focal segmental glomerulosclerosis	RCC	renal cell carcinoma
ATN	acute tubular necrosis	GBM	glomerular basement membrane	RPF	renal plasma flow
AV	atrioventricular	GFR	glomerular filtration rate	RPGN	rapidly progressive glomerulonephritis
AVM	arteriovenous malformation	GN	glomerulonephritis	RRT	renal replacement therapy
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody	HAART	highly active antiretroviral therapy	RTA	renal tubular acidosis
C&S	culture and sensitivity	HBV	hepatitis B virus	SIADH	syndrome of inappropriate antidiuretic hormone
CHF	congestive heart failure	HCTZ	hydrochlorothiazide	SLE	systemic lupus erythematosus
CKD	chronic kidney disease	HCV	hepatitis C virus	SLED	sustained low efficiency dialysis
Cr	creatinine	HPF	high power field	TBW	total body water
CrCl	creatinine clearance	HSP	Henoch-Schönlein purpura	TIN	tubulointerstitial nephritis
CV	cardiovascular	HTN	hypertension	TTP	thrombotic thrombocytopenic purpura
CVVHD	continuous veno-venous hemodialysis	HUS	hemolytic uremic syndrome	UAG	urine anion gap
D5W	5% dextrose in water	IVP	intravenous pyelogram	UTI	urinary tract infection
DCT	distal convoluted tubule	LOC	level of consciousness		
DDAVP	1-desamino-8-d-arginine vasopressin	MDRD	modification of diet in renal disease		
DI	diabetes insipidus				

Basic Anatomy Review

Embryology of the Kidney

- originates from urogenital ridge of the intermediate mesoderm
- pronephros develops at the end of wk 3, then degenerates along with adjacent pronephric duct, disappearing completely by end of wk 4
- mesonephros develops caudal to the pronephros in wk 4, degenerates, and the remnants form the mesonephric (Wolffian) duct of the male reproductive system
- metanephros develops caudal to the mesonephros in wk 5 from the metanephric blastema and the ureteric bud of the mesonephric duct, forming the definitive kidney
  - excretory system: metanephric blastema → nephrons (i.e. glomeruli, Bowman's capsule, PCT, loop of Henle, DCT)
  - collecting system: ureteric bud → collecting ducts, calyces, renal pelvis, ureters
  - kidneys ascend from the pelvis into the retroperitoneum, gaining a blood supply from the abdominal aorta to form the renal arteries

Renal Structure and Function

The Nephron

- basic structural and functional unit of the kidney, approximately 1 million per kidney
- 2 main components: glomerulus and attached renal tubule
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

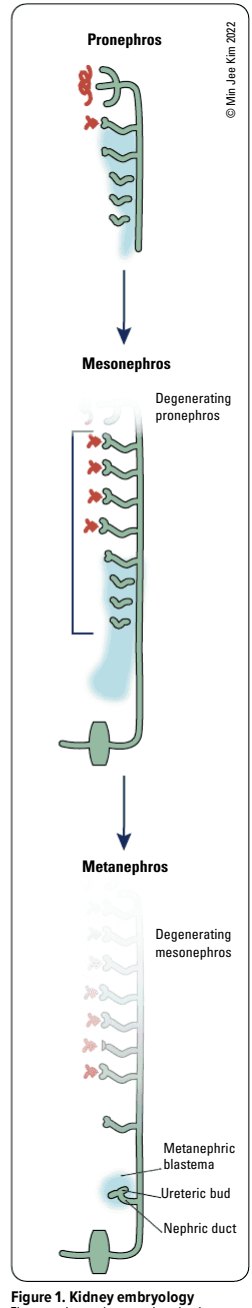

Figure 1. Kidney embryology
The pronephros and mesonephros develop then degenerate in succession. Ultimately, the definitive kidney develops from the metanephric blastema and ureteric bud of the mesonephric duct

Table 1. Major Kidney Functions

Function	Mechanism	Affected Elements
1. Waste Excretion	Glomerular filtration	Excretion of nitrogenous products of protein metabolism (urea, Cr)
	Tubular secretion	Excretion of organic acids (urate) and organic bases (Cr)
	Tubular catabolism	Breakdown and excretion of drugs (antibiotics, diuretics) and peptide hormones (most pituitary hormones, insulin, glucagon)
2. Electrolyte Balance and Osmoregulation	Tubular NaCl and water reabsorption	Controls volume status and osmolar balance
	Tubular K^+ secretion	Controls potassium concentration
	Tubular H^+ secretion	Acid-base balance
	HCO_3^- synthesis and reabsorption	Acid-base balance
	Tubular Ca^{2+}, Mg^{2+}, PO_4^{3-} transport	Alters Ca^{2+}, Mg^{2+}, PO_4^{3-} homeostasis
	Osmolyte synthesis	Increase osmolality of medullary cytoplasm to match medullary concentration gradient
3. Hormonal Synthesis	Erythropoietin production (cortex)	Red blood cell production
	Vitamin D activation: 25(OH)Vitamin D converted to 1,25(OH)2Vitamin D (proximal tubule)	Calcium homeostasis
	Renin production (juxtaglomerular apparatus)	Alters vascular resistance and aldosterone secretion
4. Blood Pressure Regulation	Na+ excretion	Alters ECF volume
	Renin production	Alters vascular resistance
5. Glucose Homeostasis	Gluconeogenesis (from lactate, pyruvate, and amino acids)	Glucose supply maintained in prolonged starvation
	Clearance and degradation of circulating insulin	Maintains glucose homeostasis

The Glomerulus

- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman's space
- there is a filtration barrier to large negatively charged molecules, e.g. albumin
- consists of following cell types:
  1. mesangial cells
     - structural function: support glomerular capillaries; can alter GFR through contractile activity
     - secretory function: matrix components, pro- and anti-inflammatory cytokines, and chemokines
     - secretions are responsible for minimizing the accumulation of macromolecules in the mesangial space and GBM
  2. capillary endothelial cells
     - part of the glomerular filtration barrier; help form the plasma filtration apparatus due to their fenestrated nature and glycocalyx; contribute to the production of the GBM
     - interface with blood – target for antibodies and contact site for neutrophils and lymphocytes
  3. visceral cells (podocytes)
     - part of the glomerular filtration barrier; helps form the plasma filtration apparatus due to their interdigitated foot process forming slit diaphragms; contribute to the production of extracellular matrix proteins (collagen and laminin) making up the GBM
  4. parietal cells
     - lines the interior of Bowman's capsule and contains a podocyte progenitor population
  5. juxtaglomerular cells
     - smooth muscle cells in the lining of afferent arteriole, adjacent to the macula densa cells in the distal tubule; produce, store, and secrete renin

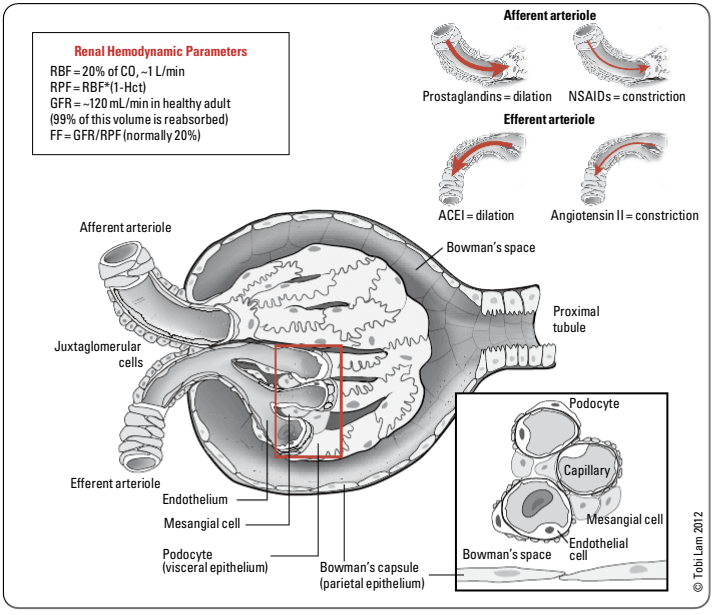

Figure 2. The glomerulus

The Renal Tubules

- reabsorption and secretion occur between the renal tubules and vasa recta, forming urine for excretion
- each segment of the tubule selectively transports various solutes and water, and is targeted by specific diuretics

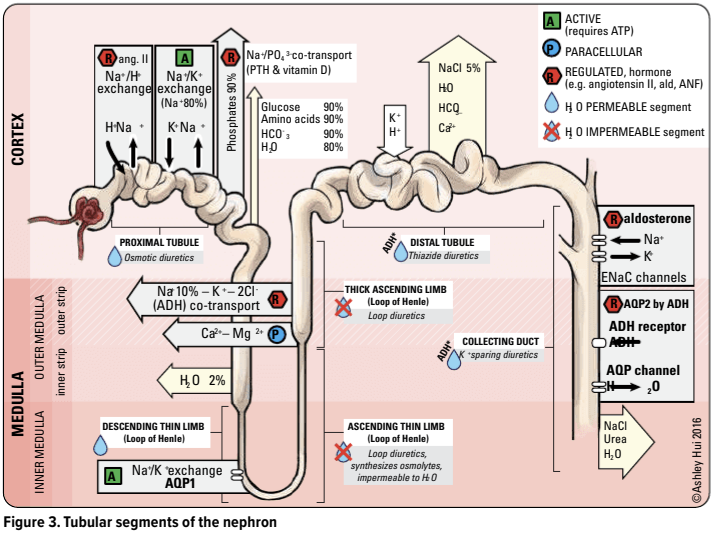

Figure 3. Tubular segments of the nephron

Renal Hemodynamics

- GFR
  - GFR is the rate of fluid transfer between glomerular capillaries and Bowman's space, expressed as the sum of the filtration across all nephrons
  - average GFR of 180 L/d or 125 mL/min/1.73 m ^{2}, of which 99% of the filtrate is reabsorbed
  - normal urine output is 0.5-2.0 mL/kg/h in adults
  - GFR is highest in early adulthood, and decreases thereafter starting around age 40
- renal autoregulation maintains constant GFR over mean arterial pressures of 70-180 mmHg
- 2 mechanisms of autoregulation to maintain GFR homeostasis:
  - myogenic mechanism: release of vasoactive factors in response to changes in perfusion pressure (e.g. low GFR → decreased perfusion pressure → release of prostaglandin → afferent arteriolar dilation → increased GFR)
  - tubuloglomerular feedback: changes in Na^+ delivery to macula densa lead to changes in afferent arteriolar tone (e.g. high GFR → increased Na^+ delivery → afferent constriction → decreased GFR)
- filtration fraction
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio: FF = GFR/RPF; normal = 0.2 or 20%
  - angiotensin II constricts renal efferent arterioles which increases FF, thereby maintaining GFR
- renin is released from juxtaglomerular apparatus in response to low Na^+ delivery to the macula densa, which is an indicator of decreased RPF
  - renin is an important enzyme in the RAAS pathway, that converts angiotensinogen to angiotensin I

Glomerular Filtration Rate	
GFR	Kf (ΔP – ΔΠ)
Kf	ultrafiltration coefficient
ΔP	hydrostatic pressure difference between glomerular capillaries and Bowman's space
ΔΠ	osmotic pressure difference between glomerular capillaries and Bowman's space
ΔP – ΔΠ	net outward pressure

Considerable variation in GFR is observed based on age, biological sex, ethnicity, and BMI

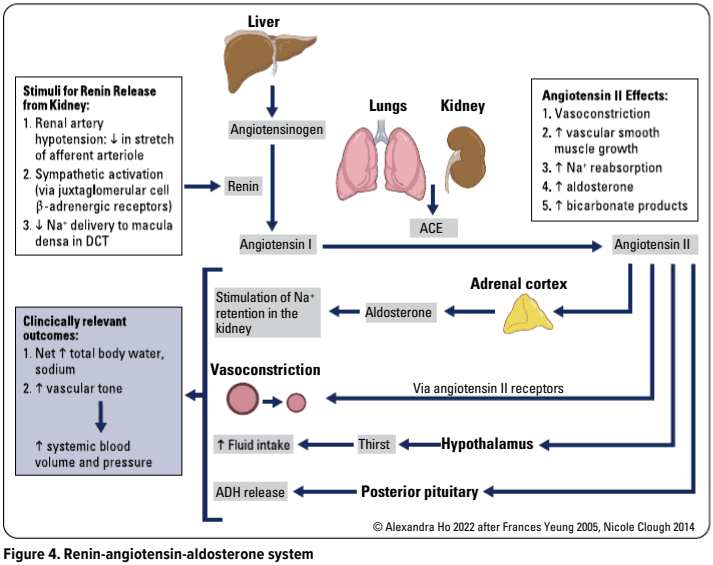

Figure 4. Renin-angiotensin-aldosterone system

Assessment of Renal Function

Measurement of Renal Function

- most renal functions decline in parallel with a decrease in GFR
- inulin clearance and iothalamate radiotracer are the gold standard for measuring GFR, but very rarely used clinically
- clinically, GFR is estimated using serum creatinine concentration, [Cr], known as eGFR
  - Cr filtered ≈ Cr excreted (at steady state)
  - Cr reasonably estimates GFR as it is freely filtered at the glomerulus with little tubular reabsorption

Crfiltered = Crexcreted
[Cr]plasma x GFR = [Cr]urine x urine flow rate (mL/min)
GFR = $\frac{[Cr]urine \times urine\ flow\ rate}{[Cr]plasma}$

- however, Cr is a metabolite of creatine phosphate, and therefore increased muscle mass increases Cr production. Thus, one needs to consider body mass, ethnicity, age, and biological sex when determining eGFR
- there is also 10% to >50% tubular secretion of Cr, depending on renal function

- newly discovered biomarkers such as Cystatin C, which are not affected by muscle mass, may provide more accurate eGFR values

Ways to Estimate GFR Using Serum Creatinine Concentration

1. estimate GFR using CKD-EPI equation
   - the best current and most accurate equation
   - calculated using serum Cr, age, biological sex, and race
   - equation performance improves at low GFR
2. measure CrCl – 24 h urine collection
   - calculation provides reasonable estimate of GFR
   - GFR/d = (urine [Cr] x 24 h urine volume)/(plasma [Cr])
   - must use same units for urine [Cr] and plasma [Cr]
3. estimate GFR with new Cr and cystatin C-based equations
   - serum Cr and cystatin C values used with age and sex to estimate GFR (excludes the race variable)
   - more accurate than CKD-EPI with race omitted

Limitations of Using Serum Cr Measurements

1. must be in steady state
   - constant GFR and rate of production of Cr from muscles
   - sudden kidney injury (e.g. AKI) may reduce GFR substantially, however, serum Cr will not immediately reflect sudden reduction in GFR until new Cr steady state is reached
2. GFR must fall substantially before plasma [Cr] rises above normal laboratory range due to compensatory factors
   - with progressive renal failure, remaining nephrons compensate with vascular autoregulation and hyperfiltration
   - GFR is relatively preserved despite significant structural damage
3. plasma [Cr] is influenced by the rate of Cr production
   - lower production with smaller muscle mass (e.g. female, elderly, low weight)
     - e.g. consider plasma [Cr] of 100 µmol/L in both of these patients
       - 20 yr lean man who weighs 100 kg, GFR = 144 mL/min
       - 80 yr woman who weighs 50 kg, GFR = 30.6 mL/min
   - clinical correlation: GFR decreases with age but would not be reflected as a rise in serum Cr due to the age-associated decline in muscle mass
4. tubular secretion of Cr increases as GFR decreases
   - serum Cr and CrCl overestimate low GFR
   - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
5. errors in Cr measurement (in older lab evaluation methods)
   - very high bilirubin level causes [Cr] to be falsely low
   - acetoacetate (a ketone body) and certain drugs (cefoxitin) create falsely high [Cr]

Measurement of Urea Concentration

- urea is the major end-product of protein metabolism
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) causes increase in urea level
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in hypernatremic states
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mmol/L for urea and µmol/L for Cr)

Urinalysis

- use dipstick in freshly voided urine specimen to assess the following:

1. Specific Gravity

- ratio of the mass of equal volumes of urine/H_2O
- range is 1.001-1.030
- values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
- value usually 1.010 (isosthenuria: same specific gravity as plasma) in CKD

2. pH

- urine pH is normally between 4.5-8.0; if persistently alkaline, consider
  - RTA (types I-IV)
  - UTI with urease-producing bacteria (e.g. *Proteus*)

At steady state [Cr]serum α 1/CrCl

CKD-EPI Equation
eGFR (mL/min/1.73 m²) = 141 x min(SCr/κ, 1)α x max(SCr/κ, 1)$^{-1.209}$ x 0.993age
x (1.018 if female) x (1.159 for Black individuals)
[SCr] measured in mg/dL; 1 mg/dL [Cr] = 88.4 µmol/L
κ = 0.7 for females and 0.9 for males
α = -0.329 for females and -0.411 for males
min/max indicates the minimum/maximum of SCr/κ or 1

Cystatin C
Cystatin C is a renal biomarker shown to be potentially superior to serum Cr in determining eGFR and detecting impaired filtration rate. However, its clinical use remains limited pending increased adoption and testing availability

Clinical Settings in which Urea Level is Affected Independent of Renal Function

Disproportionately High Urea

Volume depletion (prerenal azotemia)
GI hemorrhage
High protein diet
Sepsis
Catabolic state with tissue breakdown
Corticosteroid or cytotoxic agents

Disproportionately Low Urea

Low protein diet
Liver disease

Estimating Urine Osmolality
Last 2 digits of the specific gravity x 30 = urine osmolality approximately
(e.g. specific gravity of 1.020 = 600 mOsm)

3. Glucose
- freely filtered at glomerulus and reabsorbed in proximal tubule
- causes of glycosuria include:
  1. hyperglycemia >9-11.1 mmol/L leads to filtration that exceeds tubular resorption capacity
  2. increased GFR (e.g. pregnancy: the proximal convoluted tubule is unable to reabsorb the glucose and amino acids)
  3. proximal tubule dysfunction (e.g. Fanconi's syndrome)
  4. sodium-glucose cotransporter 2 (SGLT2) inhibitors (i.e. -flozin drugs) which are prescribed for DM2; lower the threshold for glucosuria by preventing glucose reabsorption from the filtrate

24 h Urine Collection
Discard first morning specimen
Collect all subsequent urine for the next 24 h
Refrigerate between voids
Collect second morning specimen

4. Protein
- dipstick only detects albumin; other proteins (e.g. Bence-Jones (monoclonal light chains), immunoglobulins, Tamm-Horsfall) may be missed
- microalbuminuria (morning ACR of 2.0-20 mg/mmol) is not detected by standard dipstick; greater than these ranges would be macroalbuminuria
- gold standard: 24 h timed urine collection for total protein
- urine PCR and ACR can estimate proteinuria and albuminuria respectively. To approximate 24 h urine albumin excretion, multiply ACR by 10 for women and by 15 for men

Positive dipstick for leukocyte esterase and nitrites is highly specific for diagnosing a UTI

5. Leukocyte Esterase
- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation along the urinary tract including prostate, bladder, ureter, pelvis, and renal interstitium (e.g. AIN)

Nitrite Negative Bacteria
Enterococci
Staphylococci

6. Nitrites
- endogenous nitrates in urine are converted to nitrites by some bacteria (most commonly *E. coli*)
- high specificity but low sensitivity for UTI

Nitrite Positive Bacteria (usually Gram negative bacteria)
Enterobacteriaceae (e.g. *E. coli*)

7. Ketones
- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

8. Hemoglobin
- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis), and true hematuria (RBCs seen on microscopy)

Urine Microscopy

Table 2. Comparison of Urinary Sediment Findings

	Active Sediment = Suggestive of Parenchymal Kidney Disease	Bland Sediment = Less Likely Parenchymal Kidney Disease
Any one or more of the following seen on microscopy	Red cell casts	Only hyaline casts
	White cell casts	Small quantities of crystals
	Muddy-brown granular or epithelial cell casts	Small amount of bacteria
	>2 red cells per HPF	<2 red cells per HPF
	>4 white cells per HPF	<4 white cells per HPF

1. CELLS

Erythrocytes
- hematuria ≥5 RBCs per HPF
- dysmorphic RBCs and/or RBC casts suggest glomerular or nephronal in origin (e.g. proliferative GN)
- isomorphic RBCs or no casts suggest extraglomerular bleeding (e.g. bladder cancer)

Leukocytes
- pyuria = greater than upper limit of normal: >4 WBCs per HPF
- indicates inflammation or infection
- if persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, allergic cystitis, interstitial cystitis, papillary necrosis, renal tuberculosis, viral infections, *N. gonorrhoeae, C. trachomatis* infection

Eosinophils
- detected using Wright's or Hansel's stain (not affected by urine pH)
- consider AIN, atheroembolic disease

Oval Fat Bodies
- tubular epithelial cells or macrophages laden with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

2. CASTS

- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein
- casts originate only from the nephron

Table 3. Interpretation of Casts

Casts	Interpretation
Hyaline Casts	Physiologic (concentrated urine, fever, exercise)
Granular Casts	CKD ATN (less specific)
RBC Casts	Glomerular bleeding (proliferative GN, vasculitis)
WBC Casts	Infection (pyelonephritis) Inflammation (interstitial nephritis)
Pigmented Granular Casts (heme granular casts, muddy brown)	ATN Acute proliferative GN
Fatty/Lipid Casts	Nephrotic syndrome (proteinuria >3.5 g/d)

3. CRYSTALS

- uric acid (rosette shaped or needle shaped): consider acidic urine, hyperuricosuria, tumour lysis syndrome
- calcium phosphate: alkaline urine
- calcium oxalate (envelope shaped): consider hyperoxaluria, ethylene glycol poisoning, nephrolithiasis
- sulfur: sulfa-containing antibiotics
- triple phosphate (coffin-lid shaped): consider UTI -Kelbsiella
- acyclovir

Urine Biochemistry

- commonly measure: Na^+, K^+, Cl^-, osmolality, and pH
- 24 h urine collection more reflective of mineral balance
- no "normal" values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient's current state, for example:
  1. ECF volume depletion: expect low urine [Na^+] (kidneys should be retaining Na^+)
     - urine [Na^+] >20 mmol/L suggests a tubular injury or the action of a diuretic
     - urine [Na^+] <20 mmol/L suggests a prerenal problem
  2. daily urinary potassium excretion rate should be decreased (<20 mmol/d) in hypokalemia
     - if higher than 20 mmol/d, suggests renal contribution to hypokalemia or action of a diuretic
- osmolality is useful to estimate the kidney's concentrating ability
- FE_{Na} refers to the fractional excretion of Na^+ (Na excreted in urine/Na filtered through kidney)
  - FE_{Na} <1% suggests the pathology is prerenal
- urine pH is useful to grossly assess renal acidification
  - low pH (<5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (e.g. RTA Type 1)

Fractional Excretion of Sodium

$$FE_{Na} = \frac{[Na^+]_{urine} \times [Cr]_{plasma}}{[Na^+]_{plasma} \times [Cr]_{urine}} \times 100$$

Electrolyte Disorders

Sodium Homeostasis

- hyponatremia and hypernatremia are disorders of water balance
  - hyponatremia usually suggests too much water in the ECF relative to Na^+ content
  - hypernatremia usually suggests too little water in the ECF relative to Na^+ content
- solutes (such as Na^+, K^+, glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
  - water moves out of cells in response to increased ECF osmolality
  - water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by Na^+ content rather than concentration
  - Na^+ deficiency leads to ECF volume contraction
  - Na^+ excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially brain cells) shrinking (hypernatremia) or swelling (hyponatremia)

Table 4. Clinical Assessment of ECF Volume* (Total Body Na^+)

Fluid Compartment	Hypovolemic	Hypervolemic
Intravascular		
JVP	Decreased	Increased
Blood pressure	Orthostatic drop	Normal to increased
Auscultation of heart	Tachycardia	S3
Auscultation of lungs	Normal	Inspiratory crackles
Interstitial		
Skin turgor	Decreased	Normal/increased
Edema (dependent)	Absent	Present
Other		
Urine output	Decreased**	Variable
Body weight	Decreased	Increased
Hematocrit, serum protein	Increased	Decreased
Urine sodium	Increased/Decreased***	Decreased
IVC size****	≤2.1 cm	>2.1 cm
IVC collapse on inspiration	>50%	<50%

*Refers to effective circulating volume (ECV), which is the ECF volume perfusing tissues
**If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia
***In hypovolemia, urine sodium can be increased due to renal losses, or decreased due to extra-renal losses
****IVC ultrasound during respiration assesses central venous pressure/right atrial pressure; lung ultrasound for B-lines can also be used for assessment of pulmonary congestion

Hyponatremia

Definition

- serum [Na +] <135 mmol/L
- can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality
- consider if it is associated with "appropriate" (hypovolemia) vs. "inappropriate" (euvolemia) ADH secretion
- if appropriate ADH secretion, is it real vs. effective volume loss?

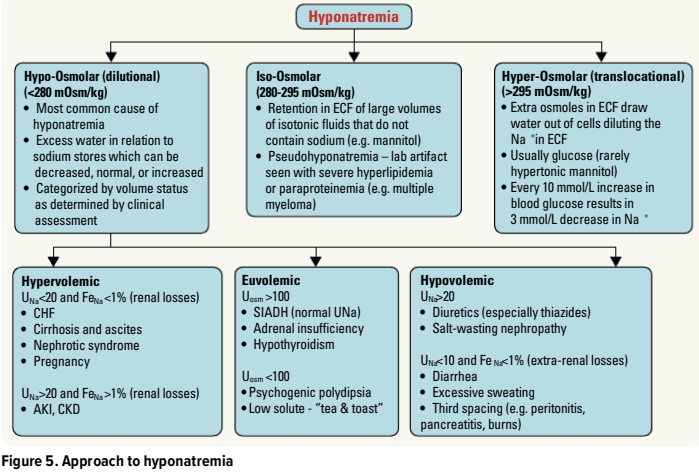

Figure 5. Approach to hyponatremia

If the urine osmolality is unknown, assume the urine is hypo-osmolar/dilute

Hypovolemic hyponatremia -H_2O loss < Sodium loss
Hypervolemic hyponatremia -H_2O gain > Sodium gain
Euvolemic hyponatremia -H_2O gain, neutral sodium balance

Signs and Symptoms

- depend on degree of hyponatremia and, more importantly, velocity of progression from onset
- hyponatremia = swollen cells
- acute hyponatremia (<48 h) more likely to be symptomatic
- chronic hyponatremia (>48 h) less likely to be symptomatic due to adaptation
  - adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days)
- neurologic symptoms predominate (secondary to cerebral edema): headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased LOC

Symptoms of Central Pontine Myelinolysis
Cranial nerve palsies
Quadriplegia
Decreased LOC

Complications of Acute Hyponatremia

- cerebral edema and increased intracranial pressure resulting in nausea, headaches, decreased LOC, seizures, coma, brain herniation, and death

Correction of Na^+ in hyponatremia should not exceed 8 mmol/L/24 h unless definitely known to be <24-48 h duration; frequent monitoring of serum Na+ and urine output is essential

- risk of brain cell shrinkage with rapid correction of hyponatremia
  - can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible (e.g. central pontine myelinolysis)
  - symptom onset may be delayed 2-6 d; begins as dysarthria, dysphagia, paresis, movement disorders → later on seizures, lethargy, confusion, disorientation, obtundation, coma

Risk Factors for Osmotic Demyelination

- low serum [Na^+] of ≤115 mmol/L at presentation and/or duration of hyponatremia ≥2 d
- associated hypokalemia, malnutrition, liver disease, alcoholism
- overly rapid correction of [Na^+], i.e. rise in [Na^+] >8 mmol/L/24 h if chronic hyponatremia, e.g.:
  - inappropriate sodium replacement
  - restoration of euvolemia leading suppression of ADH by restoring euvolemia with isotonic fluid, or by stopping a reversible stimulus of SIADH (organic disorders; medications e.g. SSRIs; limbic system activation e.g. nausea, pain, surgical stress; see *Table 5, NP11*)
  - discontinuation of thiazides; depriving water in patient with psycgenic polydipsia

Investigations for Hyponatremia

- ECF volume status assessment (see *Table 4, NP9*)
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine Na^+ (urine Na^+ <10-20 mmol/L suggests volume depletion as the cause of hyponatremia)
- assess for causes of SIADH (see *Table 5, NP11*)
- TSH, free T4, and cortisol levels
- consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. paraneoplastic syndrome by small cell lung cancer)
- consider CT head if suspect CNS cause of SIADH (e.g. subarachnoid hemorrhage)

Beware of Rapid Correction of Hyponatremia

Rapid correction of hyponatremia can occur inadvertently, commonly after stopping a reversible secondary cause of SIADH, e.g.:

Patient with SIADH secondary to nausea is given an anti-emetic

Resolution of nausea causes a rapid cessation of SIADH, leading to renal excretion of excess water and rapid increase in serum [Na+]

Patient at risk of osmotic demyelination

High output dilute urine (>100 cc/h, <100 mOsm/L) in the setting of hyponatremia is usually the first sign of dangerously rapid correction of serum sodium

Treatment of Hyponatremia

- general measures for all patients
  1. restrict free water intake (<500-1500 ml/d depending on severity of hyponatremia)
  2. treat underlying cause (e.g. restore ECF volume if volume depleted, remove offending drug, treat pain, nausea, etc.)
  3. if euvolemic or hypervolemic hyponatremia, promote free water loss - furosemide or urea tablets
  4. carefully monitor serum Na^+, urine volume, and urine osmolality
  5. frequent monitoring for rapid overcorrection - brisk urine output (free water diuresis), frequent urine and serum electrolytes
- monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia as the stimulus for ADH is diminished with the correction of hypovolemia

Concentration of [Na^+] in Common Infusates

- [Na^+] in 0.45% NaCl = 77 mmol/L
- [Na^+] in 0.9% NaCl = 154 mmol/L
- [Na^+] in 3% NaCl = 513 mmol/L
- [Na^+] in 5% NaCl = 855 mmol/L
- [Na^+] in Ringer's lactate = 130 mmol/L
- [Na^+] in D5W = 0

A. Known Acute (known to have developed over <48 h)

- commonly occurs in hospital (dilute IV fluid, postoperative increased ADH)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
  - correct rapidly with 3% NaCl at 1-2 cc/kg/h up to serum [Na^+] = 125-130 mmol/L
  - may need furosemide to address volume overload
- if asymptomatic, treatment depends on presence of risk factors for ODS and volume status (see next section)
  - goal is to promote a negative balance of free water
  - restrict free water intake
  - promote free water loss by administration of furosemide with salt tablets, oral urea, or vasopressin receptor 2 antagonists (e.g. tolvaptan)
  - if ODS risk factors present, aim to correct serum sodium more slowly
  - do not give 3% NaCl if hyponatremia is autocorrecting due to water diuresis

B. Chronic and Asymptomatic

1. if severe symptoms (seizures or decreased LOC)
   - must partially correct acutely
   - aim for increase of Na^+ by 0.5-1 mmol/L/h for 4-6 h
   - limit total rise to 8 mmol/L in 24 h
   - IV 3% NaCl at 1-2 cc/kg/h
   - may need furosemide
2. if asymptomatic
   - water restrict to <1 L/d fluid intake
   - consider IV 0.9% NS + furosemide (reduces urine osmolality, augments excretion of H_2O)
   - consider NaCl tablets as a source of Na^+
3. refractory
   - furosemide and oral salt tablets
   - oral urea (osmotic aquaresis)
   - vasopressin receptor 2 antagonists (e.g. tolvaptan)
4. always pay attention to patient's ECF volume status – if already volume-expanded, usually don't give NaCl (tablet or IV); if already volume-depleted, almost never appropriate to give furosemide

C. Options for Treatment of Overly-Rapid Correction

- give water (IV D5W)
- give DDAVP (synthetic ADH analogue) to stop water diuresis (DDAVP 1-4 μg IV q8H as needed)

Impact of IV Solution on Serum [Na+]
- formula to estimate the change in serum [Na +] caused by retention of 1 L of any infusate
- [TBW = (for men) 0.6 x weight(kg); (for women) 0.5 x weight(kg)]

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION
1. urine that is inappropriately concentrated for the serum osmolality
2. urine sodium >20-40 mmol/L – likely reflecting euvolemia
3. FE_{Na} >1%

Table 5. Disorders Associated with SIADH

Cancer	Pulmonary	CNS	Drugs	Miscellaneous
Small cell cancer Bronchogenic carcinoma Pancreatic adenocarcinoma Hodgkin's lymphoma Thymoma Leukemia	Pneumonia Lung abscess Tuberculosis Acute respiratory failure Asthma COPD Positive pressure ventilation	Mass lesion Encephalitis Subarachnoid hemorrhage Stroke Head trauma Acute psychosis Acute intermittent porphyria	Antidepressants TCAs SSRIs Antineoplastics Vincristine Cyclophosphamide Anti-epileptics Carbamazepine Barbiturates Chlorpropamide ACEI Other DDAVP Oxytocin Nicotine	Postoperative state Pain Severe nausea HIV

Hypernatremia

Definition
- serum [Na +] >145 mmol/L
- too little water relative to total body Na +; always a hyperosmolar state
- usually due to NET water loss or insufficient intake, rarely due to hypertonic Na +gain
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

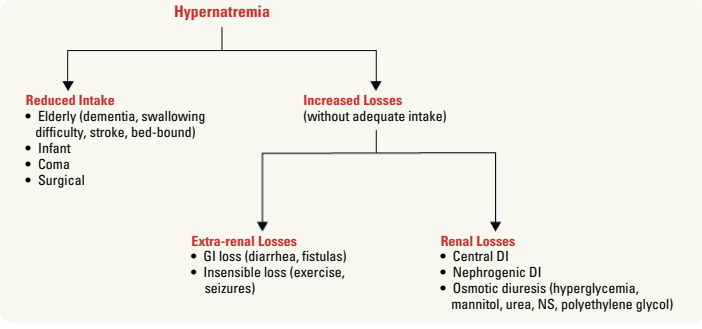

Figure 6. Approach to hypernatremia

Signs and Symptoms
- hypernatremia = shrunken cells
  - acute hypernatremia (<48 h)
  - chronic hypernatremia (>48 h), cells will have achieved adaptive mechanism: can import and generate new osmotically active particles to normalize cell size
  - nearly all cases of hypernatremia will be due to chronic hypernatremia
  - acute hypernatremia primarily presents in patients with diabetes insipidus, post obstructive diuresis, and post ATN diuresis (without free water access)
  - symptoms due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- ± polyuria, thirst, signs of hypovolemia

Complications
- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema

H_2O Deficit and TBW Equations
TBW = 0.6 x wt (kg) men
TBW = 0.5 x wt (kg) women

H_2O deficit = TBW x ([Na^+]plasma – 140) / 140

Correction of serum [Na^+] in hypernatremia should not exceed 12 mmol/L/24 h

1 L D5W approximately equals 1 L of free water
1 L 0.45% NS approximately equals 500 mL of free water

Outcomes in Severe Hyponatremia Treated With and Without Desmopressin
Am J Med 2018;131:1-317
Purpose: Rapid overcorrection of plasma Na+ in severe hyponatremia can lead to osmotic demyelination syndrome. This study seeks to compare outcomes in hyponatremia based on DDAVP usage in treatment.
Methods: Retrospective study including all admissions to internal medicine with hyponatremia (plasma Na+ <123 mEq/L) from 2004 to 2014 at 2 Toronto hospitals. The primary outcome was safe Na+ correction (<12 mEq/L in any 24 h period and <18 mEq/L in any 48 h period), time to reach Na+ >130 mEq/L or hospital discharge. DDAVP uses were excluded for DI and for bleeding prevention in thrombocytopenia.
Results: Among 1450 admissions of 1274 patients for hyponatremia over the 10 yr period, desmopressin was administered in 254 admissions (17.5%). Fewer patients receiving DDAVP achieved safe Na+ correction within the 24 h time frame (70.9% vs. 85%; P<0.001). The proportion of cases with safe Na+ correction was highest in the proactive-DDAVP treatment group, followed by reactive then rescue treatment (78.6% for proactive vs. 29.3% for reactive). According to clinical or radiographic findings, 4 of 1450 admissions had suspected osmotic demyelination syndrome, two of which occurred during DDAVP administration (0.79% incidence, 95% CI 0.22-2.82).
Conclusions: The rescue strategy of DDAVP administration is not an ideal strategy, while the proactive strategy was effective at slowing Na+ rate of change. In patients at risk for osmotic demyelination syndrome, a proactive DDAVP strategy more often achieved a more stringent correction limit.

Treatment of Hypernatremia

- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum Na^+ frequently (q4h) to ensure correction is not occurring too rapidly
- if evidence of hemodynamic instability, then must first correct volume depletion with NS bolus
- loss of water is often accompanied by loss of Na^+, but a proportionately larger water loss
- encourage patient to drink pure water, as PO is preferred for fluid administration
- if unable to replace PO or NG, correct H_2O deficit with hypotonic IV solution (IV D5W, 0.45% NS [half normal saline], or 3.3% dextrose with 0.3% NaCl ["2/3 and 1/3"])
- chronic hypernatremia: aim to lower serum sodium by 8-10 mEq/L in 24 h (often achieved by giving free water at 1.35 mL/kg/h)
- acute hypernatremia: use formula to calculate water deficit. Replace entire water deficit within 24 h (hourly infusion rate = water deficit in mL/24 h)
- infusion rate may need to be increased in order to account for ongoing losses in addition to initial deficit

Diabetes Insipidus

Definition

- collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
- defect in central release of ADH (central DI) or renal response to ADH (nephrogenic DI)

Etiology

- central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
- nephrogenic DI
  - usually acquired – drugs (e.g. lithium), secondary to amyloidosis, sickle cell disease, Sjogren syndrome, polycystic kidney disease, electrolyte imbalances (i.e. hypercalcemia)
  - congenital/hereditary
  - post ATN diuresis
  - post obstructive diuresis

Diagnosis

- urine osmolality inappropriately low in patient with hypernatremia (U_{osm} <300 mOsm/kg)
- serum vasopressin concentration may be absent/low (central), or elevated (nephrogenic)
- dehydration test: H_2O deprivation until loss of 3% of body weight or until urine osmolality rises above plasma osmolality and/or Na increases over 146; if urine osmolality remains <300 (fails to concentrate urine), most likely DI

Management

- central DI: administer exogenous ADH (e.g. DDAVP) 10 µg intranasally or 2 µg SC or IV
- nephrogenic DI: patients may have partial or complete ADH resistance, and DDAVP is generally ineffective
  - maintain fluid intake to match losses, e.g. PO water, IV D5W, IV 0.45% NS
  - treat underlying cause of nephrogenic DI
  - thiazides can help by paradoxically reducing urine output: thiazides induce hypovolemia → stimulate proximal tubular reabsorption of sodium and water → less delivery of glomerular filtrate to the collecting duct → lower urine volume

A Copeptin-Based Approach to the Diagnosis of Diabetes Insipidus
NEJM 2018;379:428-39
Purpose: Comparison of the indirect water-deprivation test, a technically cumbersome test, with direct detection of plasma copeptin, a precursor-derived surrogate of arginine vasopressin.
Methods: From 2013 to 2017, 156 patients with hypotonic polyuria underwent both indirect water-deprivation testing and hypertonic saline infusion tests. In the latter test, plasma copeptin levels were measured when plasma Na+ increased to >150 mmol/L after saline infusion. The primary outcome was overall diagnostic accuracy of each test compared with final reference diagnosis, as determined by clinical history, test results and treatment response, with copeptin levels masked.
Results: Among the 141 patients included in final analysis, the indirect water-deprivation test showed diagnostic accuracy in 108 patients (76.6%; 95% CI 68.9 to 83.2) and the hypertonic saline infusion (copeptin cutoff >4.9 mmol/L) showed diagnostic accuracy in 136 patients (96.5%; 95% CI 92.1 to 98.6, P<0.001). The water-deprivation test correctly distinguished primary polydipsia from partial central DI in 77 of 105 patients (73.3%; 95% CI 63.9 to 81.2) while the hypertonic saline test distinguished in 99 of 104 patients (95.2%; 95% CI 89.4 to 98.1, P<0.001).
Conclusion In patients with hypotonic polyuria, direct measurement of hypertonic-saline stimulated plasma copeptin levels showed greater diagnostic accuracy than the water-deprivation test.

Potassium Homeostasis

- ~98% of total body K^+ stores are intracellular
- normal serum K^+ ranges from 3.5-5.0 mEq/L
- in response to K^+ rise, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia (K+ >6.5 mEq/L)
- insulin, catecholamines, and acid-base status influence K^+ movement into cells
  - aldosterone has a minor effect
- potassium excretion is regulated at the DCT and collecting ducts
  - K^+ excretion = urine flow rate x urine $[K^+]$

Factors which Increase Renal K^+ Loss

- hyperkalemia
- increased distal tubular urine flow rate and Na^+ delivery (thiazides and loop diuretics)
- increased aldosterone activates epithelial sodium channels in cortical collecting duct, causing Na^+ reabsorption and K^+ excretion
- metabolic alkalosis (increases K^+ secretion)
- hypomagnesemia
- increased non-resorbable anions in tubule lumen: HCO_3^-, penicillin, salicylate (increased tubular flow rate increases K^+ secretion)

Hypokalemia

Definition

- serum [K^+] <3.5 mEq/L

Signs and Symptoms

- usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
- nausea/vomiting, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
- if severe: arrhythmias, rhabdomyolysis, myoglobinuria, and rarely paralysis with eventual respiratory impairment
- arrhythmias occur at variable levels of K^+; more likely with digoxin use, hypomagnesemia, or CAD
- ECG changes are more predictive of clinical picture than serum [K^+]
  - U waves most important (low amplitude wave following a T wave)
  - flattened or inverted T waves
  - depressed ST segment
  - prolongation of Q-T interval
  - sinus bradycardia
  - with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity
  - common arrhythmias seen with hypokalemia: ventricular fibrillation, ventricular tachycardia

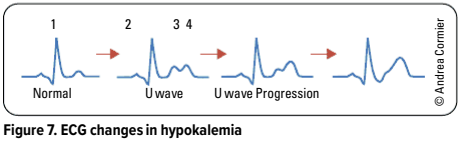

Figure 7. ECG changes in hypokalemia

Approach to Hypokalemia

1. emergency measures if K^+<2.5 mEq/L: obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of K^+as cause of hypokalemia
3. assess contribution of dietary K^+ intake
4. spot urine K:Cr
   - if <1.5 mEq/mmol consider GI loss
   - if >1.5 mEq/mmol consider a renal loss
5. consider 24 h K^+excretion
6. if renal K^+loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum [Mg^{2+}]

Hypokalemia is often accompanied by metabolic alkalosis:

- K^+shifts from cells to ECF; H^+shifts into cells in response
- Plasma [HCO_3^-] increases, while intracellular pH decreases
- In response to low pH, renal tubular cells secrete H^+into lumen, and increase renal ammoniagenesis and excretion
- Resultant addition of more [HCO_3^-] into plasma → metabolic alkalosis

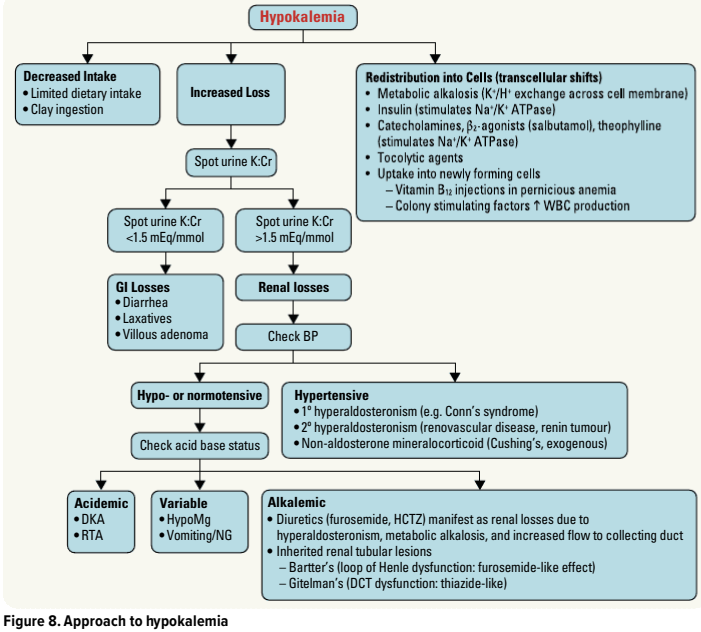
Hypokalemia
Decreased Intake
• Limited dietary intake
• Clay ingestion
Increased Loss
Redistribution into Cells (transcellular shifts)
• Metabolic alkalosis (K^+/H^+ exchange across cell membrane)
• Insulin (stimulates Na^+/K^+ ATPase)
• Catecholamines, β_2-agonists (salbutamol), theophylline (stimulates Na^+/K^+ ATPase)
• Tocolytic agents
• Uptake into newly forming cells
– Vitamin B_{12} injections in pernicious anemia
– Colony stimulating factors ↑ WBC production
Spot urine K:Cr
Spot urine K:Cr <1.5 mEq/mmol
Spot urine K:Cr >1.5 mEq/mmol
GI Losses
• Diarrhea
• Laxatives
• Villous adenoma
Renal losses
Check BP
Hypo- or normotensive
Hypertensive
• 1° hyperaldosteronism (e.g. Conn's syndrome)
• 2° hyperaldosteronism (renovascular disease, renin tumour)
• Non-aldosterone mineralocorticoid (Cushing's, exogenous)
Check acid base status
Acidemic
• DKA
• RTA
Variable
• HypoMg
• Vomiting/NG
Alkalemic
• Diuretics (furosemide, HCTZ) manifest as renal losses due to hyperaldosteronism, metabolic alkalosis, and increased flow to collecting duct
• Inherited renal tubular lesions
– Bartter's (loop of Henle dysfunction: furosemide-like effect)
– Gitelman's (DCT dysfunction: thiazide-like)

Figure 8. Approach to hypokalemia

Treatment
- treat underlying cause
- if true K^+deficit, potassium repletion
  - oral sources: food, tablets (K-Dur™), KCl liquid solutions (preferable route if the patient tolerates PO medications)
  - IV: usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
- max 40 mmol/L via peripheral vein, 60 mmol/L via central vein, max infusion 20 mmol/h
- K^+-sparing diuretics (triamterene, amiloride, spironolactone) can prevent renal K^+loss
- restore Mg^{2+}before correcting K^+
- if urine output and renal function are impaired, correct with extreme caution
- risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
- use ACE inhibitor or ARB for CHF (reduces angiotensin II action and therefore reduces aldosterone production)
- beware of excessive potassium repletion, especially if hypokalemia secondary to transcellular shift

Hyperkalemia

Definition
- serum $[K^+]$ >5.0 mEq/L

Signs and Symptoms
- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniagenesis and excretion and metabolic acidosis
- ECG changes and cardiotoxicity (do not correlate well with serum $[K^+]$)
- peaked and narrow T waves
- decreased amplitude and eventual loss of P waves
- prolonged PR interval
- widening of QRS and eventual merging with T wave (sine-wave pattern)
- AV block
- ventricular fibrillation, asystole

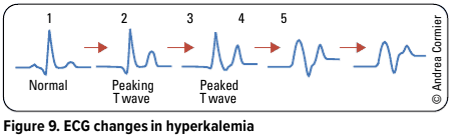

Figure 9. ECG changes in hyperkalemia

Table 6. Causes of Hyperkalemia

Pseudohyperkalemia	Increased Intake	Transcellular Shift	Decreased Excretion
Sample hemolysis*	Diet	Intravascular hemolysis	Decreased GFR
Sample taken from vein where IV KCl is running	KCl tabs	Rhabdomyolysis	Renal failure
Prolonged use of tourniquet	IV KCl	Tumour lysis syndrome	Low effective circulating volume
Leukocytosis (extreme)	Salt substitute	Insulin deficiency	NSAIDs in renal insufficiency
Thrombocytosis** (extreme)		Metabolic Acidosis	Normal GFR but hypoaldosteronism (Table 7)
		Drugs	
		β-blockers	
		Digitalis overdose (blocks Na^+/K^+ ATPase)	
		Succinylcholine	

*Most common
**Usually when blood specimen has been sitting out long before being analyzed

Table 7. Causes of Hyperkalemia with Normal GFR Secondary to Hypoaldosteronism

Decreased Aldosterone Stimulus (low renin, low aldosterone)	Decreased Aldosterone Production (normal renin, low aldosterone)	Aldosterone Resistance (decreased tubular response)
Associated with diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV	Adrenal insufficiency (e.g. Addison's disease, AIDS, metastatic cancer)	K^+-sparing diuretics:
	ACEI	Spironolactone
	Angiotensin II receptor blockers	Amiloride
	Heparin	Triamterene
	Congenital adrenal hyperplasia with 21-hydroxylase deficiency	Renal tubulointerstitial disease

Approach to Hyperkalemia
1. emergency measures: obtain ECG; if life threatening, begin treatment immediately
2. rule out pseudohyperkalemia; repeat blood test

In patients with DM and increased $[K^+]$ and hyperglycemia, often just giving insulin to restore euglycemia is sufficient to correct the hyperkalemia

3. hold exogenous K^+ (PO and IV) and any medications that are K^+ retaining
e.g. RAAS inhibitors (ACEI, ARBs), aldosterone antagonists, non-selective β-blockers (propranolol/labetalol) or affect K^+ excretion (i.e. NSAIDs)
4. assess potential causes of transcellular shift
5. determine eGFR

Treatment

- acute therapy is warranted if ECG changes are present or if patient is symptomatic regardless of $[K^+]$
- tailor therapy to severity of increase in $[K^+]$ and ECG changes
  - $[K^+]$ <6.5 and normal ECG
    - treat underlying cause, stop K^+ intake, increase the loss of K^+ via urine and/or GI tract
  - $[K^+]$ between 6.5 and 7.0, no ECG changes: add insulin to above regimen
  - $[K^+]$ >7.0 and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

1. Stabilize Myocardium

- calcium gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes hyperkalemia induced membrane depolarization, protects cardiac conduction system, no effect on serum $[K^+]$
- onset within minutes, lasts 30-60 min (may require repeat doses during treatment course of hyperkalemia)

2. Shift K^+ into Cells

- regular insulin (Insulin R) 10-20 units IV, with 50-100 mL D50W to prevent hypoglycemia
  - onset of action 15-30 min, lasts 4-6 h
  - monitor capillary blood glucose q1h because of risk of hypoglycemia
  - can repeat q4-6 h
  - caution giving D50W before or without insulin if hyperkalemia is severe: hypertonic glucose increases plasma osmolality, promoting extracellular water and $^+$shift, and can cause a serious arrhythmia
- β2-agonist (Ventolin®) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  - onset of action 30-90 min, stimulates Na^+/K^+ ATPase
  - caution if patient has heart disease as may result in tachycardia

3. Enhance K^+ Removal from Body

- via urine (preferred approach)
  - furosemide (≥40 mg IV), may need IV NS to avoid hypovolemia
  - fludrocortisone (synthetic mineralocorticoid) if suspecting aldosterone deficiency
- via GI (if renal function is severely impaired)
  - cation exchangers: patiromer 8.4 g PO OD (up to 25.2 g/d), zirconium cyclosilicate, or sodium polystyrene sulfonate (Kayexalate®)
    - practically, patiromer and zirconium are not currently widely employed due to high cost
    - sodium polystyrene sulfonate (Kayexalate®) should be used with caution, as they may lead to the development of colonic necrosis and intestinal perforation, especially when used in combination with sorbitol
  - osmotic laxatives e.g. lactulose can support GI excretion of K^+ in the form of diarrhea
- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

Treatment of Hyperkalemia

C BIG K DROP

C	Calcium gluconate
BIG	β-agonist, Insulin, Glucose
K	Kayexalate®
DROP	Diuretics, Dialysis

Acute Management of Hyperkalemia

Curr Heart Failure Rep 2019;16:67-74

Purpose: Outline and review the current evidence behind the acute medical management of hyperkalemia, including the three principal strategies of stabilizing the myocardium, intracellular shifting of serum K^+, and enhancing elimination via urinary or fecal excretion.

1. Stabilizing the Myocardium: The protective effects of Ca^{2+} salts on myocardial stabilization should be seen within 5 min of administration. Doses can be repeated in 5 min intervals if life-threatening ECG changes persist. There are concerns regarding calcium use in digoxin toxicity causing irreversible non-contractile states. No life-threatening dysrhythmias occurred within 1 h of calcium administration.
2. Intracellular Shifting of Potassium: Regular insulin has shown effectiveness at decreasing serum K^+, with IV insulin decreasing serum K^+ by 0.8 mmol/L at 1 h. The main side effect of insulin-induced hypoglycemia can be managed with IV dextrose. Albuterol has an onset within 15-30 min of administration, causing maximal decreases by 1 mmol/L at 1 h. There is little evidence to suggest that sodium bicarbonate has a role in the management of hyperkalemia, except in the case of concomitant metabolic acidosis.
3. Enhanced Excretion: Though limited evidence for acute management, it is recommended to administer loop diuretics and sodium polystyrene sulfonate to eliminate K^+. Diuretics may precipitate or worsen AKI in patients with poor volume status, while sodium polystyrene sulfonate should be used with caution due to severe GI side effects such as ulceration, bleeding, colonic ischemia/necrosis, and intestinal perforation.

Hyperphosphatemia

Definition

- serum phosphate >1.45 mmol/L
  - phosphate binds to serum calcium to create insoluble precipitates in soft tissues and blood vessels, thereby resulting in hypocalcemia
  - hypocalcemia subsequently triggers the development of secondary hyperparathyroidism in patients with advanced CKD on dialysis

Etiology

- typically results from decreased renal excretion of phosphate

Table 8. Etiology of Hyperphosphatemia

Increased Phosphate Load	Reduced Renal Clearance	Pseudohyperphosphatemia
GI intake (rectal enema, GI bleeding) IV phosphate load (K-Phos®, blood transfusion) Endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis, lactic and ketoacidosis)	Acute/chronic renal failure Hypoparathyroidism Acromegaly Tumour calcinosis (ability of kidney to specifically clear phosphate is defective)	Hyperglobulinemia Hyperlipidemia Hyperbilirubinemia

Clinical Features

- non-specific, include ectopic calcification in soft tissues and vessels, renal osteodystrophy
  - symptoms consistent with hypocalcemia

Symptoms of Hypocalcemia

Tetany
Seizures
Hypotension
QT prolongation
Papilledema
Psychiatric manifestations

Treatment
- acute: IV saline, hemodialysis if symptomatic;
- chronic: low PO_4^{3-} diet, phosphate binders (e.g. $CaCO_3$, lanthanum carbonate, sevelamer with meals)

Hypophosphatemia

Definition
- serum phosphate <0.80 mmol/L

Etiology
- acute hypophosphatemia often caused by intracellular shifts of phosphate superimposed on chronic phosphate depletion
- chronic hypophosphatemia often caused by decreased renal phosphate reabsorption
- severe chronic hypophosphatemia often caused by chronic starvation or malabsorption (e.g. in patients with alcoholism) or chronic use of phosphate binders (e.g. patients with CKD)

Table 9. Etiology of Hypophosphatemia

Inadequate Intake	Renal Losses	Excessive Skeletal Mineralization	Shift into Intracellular Fluid
Starvation Malabsorption (diarrhea, steatorrhea) Antacid use Alcoholism	Hyperparathyroidism Diuretics X-linked or autosomal dominant hypophosphatemic Rickets Fanconi syndrome Multiple myeloma Early postrenal transplant	Osteoblastic metastases Post parathyroidectomy (referred to as 'hungry bone syndrome')	Recovery from metabolic acidosis Respiratory alkalosis Starvation refeeding (stimulated by insulin)

Symptoms usually present when phosphate <0.32 mmol/L (1.0 mg/dL)
Treat asymptomatic patients if phosphate <0.32 mmol/L

Severe burns can cause hypophosphatemia due to PO_4^{3-} losses through the skin

Clinical Features
- instability of cell membranes leading to hemolytic anemia or rhabdomyolysis
- MSK weakness, respiratory depression, low cardiac output/CHF from weakened cardiac muscles: symptoms arise due to low ATP production
- neurological symptoms: irritability, encephalopathy, seizures, coma
- hematologic symptoms: hemolytic anemia, decreased release of oxygen from hemoglobin, impaired leukocyte and platelet function (leading to worsening infections/defective clotting)

Treatment
- treat underlying cause
- initiate when serum $[PO_4^{3-}]$ <0.64 mmol/L. Use PO therapy if asymptomatic, or symptomatic and $[PO_4^{3-}]$ >0.32 mmol/L. Use IV therapy if symptomatic and $[PO_4^{3-}]$ <0.32 mmol/L
  - PO PO_4^{3-}: 2-4 g/d divided BID-QID (start at 1 g/d to minimize diarrhea), encourage PO_4^{3-} rich diet
  - IV PO_4^{3-}: only for severely symptomatic patients or inability to tolerate oral therapy

Hypermagnesemia

Definition
- serum magnesium >1.05 mmol/L

Etiology
- AKI/CKD
- Mg^{2+}-containing antacids or enemas
- IV administration of large doses of $MgSO_4$ (e.g. see Obstetrics, *Preeclampsia*, OB26)

Clinical Features
- rarely symptomatic
- drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest, hypotension

Treatment
- discontinue Mg^{2+}-containing products
- 10% calcium gluconate 10-20 mL IV (Mg^{2+} -antagonist) for acute reversal of magnesium toxicity
- hemodialysis if renal failure, consider peritoneal dialysis in setting of hemodynamic compromise

Hypomagnesemia

Definition

- serum magnesium <0.70 mmol/L

Etiology

GI losses	Excess renal loss
Starvation/malabsorption	2° hyperaldosteronism due to cirrhosis and CHF
Vomiting/diarrhea	Hyperglycemia
Alcoholism	Hypokalemia
Acute pancreatitis	Hypercalcemia
	Loop and thiazide-type diuretics
	Nephrotoxic medications
	Proton-pump inhibitors
	Early postrenal transplant

You will be unable to correct hypokalemia or hypocalcemia without first supplementing magnesium if patient is hypomagnesemic

Clinical Features

- tremors, nausea and vomiting, lethargy/weakness, seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities), and arrhythmias including Torsades de Pointes

Treatment

- treat underlying cause
- encourage increased dietary intake e.g. fruits
- oral Mg^{2+}salts unless patient has seizures or other severe symptoms
- Mg^{2+}IM/IV; cellular uptake of $Mg^{2+}$is slow, therefore repletion requires sustained correction
- discontinue diuretics
  - in patients requiring diuretics, use a K^{+}-sparing diuretic to minimize magnesuria

Acid-Base Disorders

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic, renal, and CNS function
- normal concentration of $[HCO_3^-]$= 24 mEq/L (range: 21–27 mEq/L for arterial blood gas sample)
- normal pCO_2 = 40 mmHg (range: 36-44 mmHg)
- each acid-base disorder has an associated compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder (e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis)
- most commonly assessed using an arterial blood gas sample
- see Respirology, R5 for more information on respiratory acidosis/alkalosis

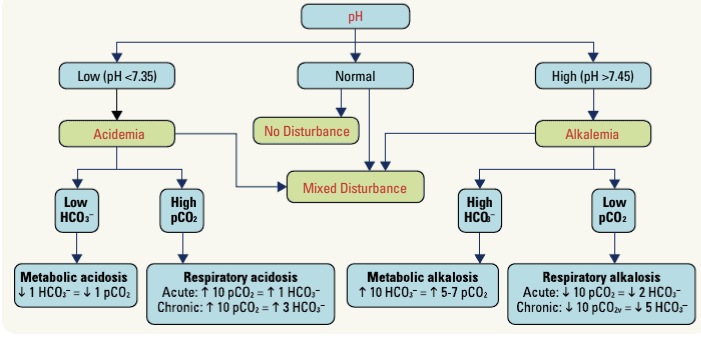

Figure 10. Approach to acid-base disorders. Equalities represent the appropriate compensatory changes in pCO_2 or HCO_3 in response to the primary disturbance

Causes of Increased Osmolar Gap

Methanol
Ethylene glycol
Ethanol
Polyethylene glycol
Mannitol
Sorbitol

Useful Equations

AG = [Na+] - [Cl^-] - [HCO_3^-] (normal range = 10-14 mEq/L)

Osmolar Gap = measured serum osmolality – calculated osmolality (normal <10 mEq/L)
– "Two Salts and a Sticky BUN"

Calculated Osmolality = 2[Na+] + [Urea] + [Glucose] (+1.25[Ethanol])

Approach

1. Identify the Primary Disturbance

- respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis

2. Evaluate Compensation. If compensation is not appropriate, second acid-base disorder is likely present

- compensation occurs in the same direction as the primary disturbance

3. Calculate Plasma AG
- AG = [Na^+] – ([HCO_3^-] + [Cl^-])
- baseline = 12, normal range 10-14 mEq/L
- AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 mEq/L (e.g. if plasma [albumin] = 20 g/L, expect AG = 6 mEq/L)
  - albumin is an unmeasured polyanion largely responsible for the normal anion gap

4. Calculate Osmolar Gap
- osmolar gap = measured osmolality – calculated osmolality
  - calculated osmolality = (2 x [Na^+]) + [urea] + [glucose] (all units are in mmol/L)
  - normal osmolar gap <10
  - If OG >10, consider methanol poisoning, ethylene glycol poisoning, or another cause of acidosis plus ethanol ingestion

5. If AG elevated, compare increase in AG with decrease in HCO_3^-b
- if increase in AG < decrease in HCO_3^-, there is a co-existing non-AG metabolic acidosis
- if increase in AG > decrease in HCO_3^-, there is a co-existing metabolic alkalosis

Metabolic Acidosis

• characterized by decreased blood pH (<7.35) and a decreased bicarbonate concentration

Clinical Features
• hyperventilation (Kussmaul Breathing)
• decreased cardiac output and tissue perfusion (reduced responsiveness to catecholamines)

Etiology and Pathophysiology
1. increased AG metabolic acidosis (4 types)
   - lactic acidosis (2 types)
     - L-lactic acid
       - type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
       - type B: non-hypoxic – multiple causes; the most common is failure to metabolize normally produced lactic acid in the liver due to severe liver disease; other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain antiretrovirals, large tumours, mitochondrial myopathies, cyanide poisoning
     - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
       - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria metabolize carbohydrate load into D-lactic acid, diminished colonic motility, and impaired D-lactate metabolism
   - ketoacidosis
     - diabetic
     - starvation
     - alcoholic (decreased carbohydrate intake and vomiting)
   - toxins
     - methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
     - ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
     - salicylate (e.g. ASA) overdose: causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacids (salicylate activates fat breakdown)
   - advanced renal failure
     - e.g. serum Cr increased at least 5x above baseline – a very low GFR causes retention of $H^+$and decreased NH_4^+ excretion; the retained acid is buffered by bicarbonate resulting in reduced serum concentrations of bicarbonate

2. non-AG metabolic acidosis (hyperchloremic acidosis; involves increased bicarbonate excretion that is replaced with Cl^-)
   - diarrhea (HCO_3^-loss from GI tract)
   - RTA
     - type I RTA (distal): inability to secrete H^+in collecting duct, leading to impaired excretion of ammonium into urine
     - type II RTA (proximal): impaired HCO_3^-reabsorption
     - type III RTA: combination of Types I and II and is extremely rare
     - type IV RTA: defective ammoniagenesis characterized by hyperkalemia, due to decreased or hyporesponsiveness to aldosterone
   - to help distinguish renal causes from non-renal causes, use Urine AG = (Na^++ K^+) – Cl^-

Causes of Increased AG Metabolic Acidosis

MUDPILES CAT
Methanol
Uremia
Diabetic ketoacidosis
Paraldehyde
Isopropyl alcohol/Iron/Ibuprofen/Indomethacin
Lactic acidosis
Ethylene glycol
Salicylates
Cyanide and Carbon monoxide
Alcoholic ketoacidosis
Toluene

Causes of Non-AG Metabolic Acidosis

HARDUP
Hyperalimentation
Acetazolamide
RTA*
Diarrhea*
Ureteroenteric fistula
Pancreaticoduodenal fistula

*Most common

3 Clinical Scenarios that Produce a Mixed Disorder with Near Normal pH (e.g. increased AG metabolic acidosis + respiratory alkalosis)
- Cirrhosis
- ASA overdose
- Sepsis

- calculation establishes the presence or absence of unmeasured positive ions (e.g. NH_4^+) in urine
  - if UAG <0, suggests adequate NH_4^+ excretion in urine (likely non-renal cause: diarrhea)
  - if UAG >0, suggests problem is lack of NH_4^+ in urine (likely renal cause: distal RTA)

Evaluation

- a detailed history and physical exam with serum or plasma electrolytes, and calculation of anion gap is usually sufficient to determine the cause of metabolic acidosis and guide therapy, but in more complicated patients measurement of pH and pCO_2 and determining whether respiratory compensation is appropriate can provide a definitive evaluation

Treatment of Metabolic Acidosis

1. treat underlying cause, e.g.:
   - in DKA: fluid resuscitation, K^+ supplementation, and insulin
   - in Type A lactic acidosis: restore tissue perfusion
   - in methanol or ethylene glycol poisoning: ethanol/fomepizole ± dialysis
   - in ASA overdose: alkaline diuresis ± dialysis
2. correct coexisting disorders of K^+ (see *Hyperkalemia, NP14*)
3. consider treatment with exogenous alkali (e.g. $NaHCO_3$) if:
   - severe reduction in $[HCO_3^-]$ e.g. <8 mmol/L, especially with very low pH (<7)
   - no metabolizable anion (e.g. salicylate, formate, oxalate, or sulphate); note that lactate and ketoacid anions can be metabolized to HCO_3^-

- note: risks of sodium bicarbonate therapy
  - hypokalemia: causes K^+ to shift into cells (correct K^+ deficit first)
  - ECF volume overload: Na^+ load given with $NaHCO_3$, can exacerbate pulmonary edema
  - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to HCO_3^-, and persisting hyperventilation

Metabolic Alkalosis

- characterized by increased blood pH (>7.45) and an increased bicarbonate concentration

Pathophysiology

- requires precipitating event and maintenance factors
- precipitating factors
  - GI (vomiting, NG tube) or renal loss of H^+
  - exogenous alkali (oral or parenteral administration), milk alkali syndrome (hypercalcemia)
  - loop/thiazide diuretics: increased distal H^+ secretion and proximal HCO_3^- reabsorption; ECF volume depletion also contributes to a contraction alkalosis
  - post-hypercapnia: renal compensation for respiratory acidosis is HCO_3^- retention, rapid correction of respiratory disorder results in transient excess of HCO_3^-
- maintenance factors
  - volume depletion: reduced GFR, increased proximal reabsorption of Na^+ and HCO3-, and increased aldosterone
  - hyperaldosteronism (1° or 2°): distal Na^+ reabsorption in exchange for K^+ and H^+ excretion leads to metabolic alkalosis and hypokalemia
  - hypokalemia: transcellular K^+/H^+ exchange, stimulus for ammoniagenesis and HCO_3^- generation

Evaluate Compensation (identify co-existing respiratory acid-base disorders)

- hypoventilation (an upper limit to compensation exists – breathing cannot be stopped)

Treatment

- correct underlying disease, replenish K^+ and Mg^{2+} deficits, and possibly K^+-sparing diuretic
- saline sensitive metabolic alkalosis (most common)
  - urine chloride <20 mEq/L, characterized by ECF contraction and hypokalemia
  - volume repletion ± carbonic anhydrase inhibitor (e.g. acetazolamide) to facilitate loss of HCO_3^- in urine
- saline resistant metabolic alkalosis
  - urine chloride >20 mEq/L, characterized by ECF expansion and hypertension (increased mineralocorticoids)
  - remove source of aldosterone or glucocorticoid ± spironolactone

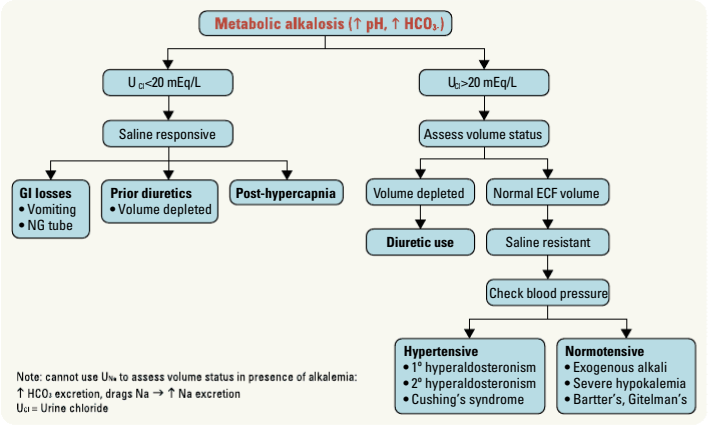

Figure 11. Approach to metabolic alkalosis

Polyuria

Definition

- output >3 L/d in adults and 2 L/m ^{2}in children. Distinguish from urinary frequency, where urination occurs multiple times per day but the total volume over 24 h is <3 L

Etiology

- either due to water diuresis or solute diuresis
- solute diuresis:
  - glucose (uncontrolled diabetes)
  - salt (increased salt intake or IV fluids with sodium)
  - urea (resolution of azotemia, intake of urea, tissue breakdown or metabolism)
- water diuresis:
  - diabetes insipidus (central or nephrogenic)
  - polydipsia (excess water drinking)
  - drugs (most commonly diuretics)

Clinical Features

- must distinguish between true polyuria and urinary frequency
- look for sources of external fluid intake (IV fluids, tube feedings)
- assess for neurological changes (stroke, trauma, postoperative) (for central diabetes insipidus). Assess for pituitary dysfunction
- assess for drugs that may cause nephrogenic diabetes insipidus (e.g. lithium)
- abrupt onset suggests central diabetes insipidus (deficient ADH)

Investigation Findings

- 24 h urine collection >3 L (in adults)
- laboratory findings that may point to specific etiologies:
  - hyperglycemia and/or glucosuria suggests osmotic diuresis secondary to uncontrolled diabetes mellitus
  - hyponatremia may suggest free water intake secondary to polydipsia
  - hypernatremia may suggest free water loss secondary to diabetes insipidus
- check urine osmolality:
  - U_{osm} <100 mOsm/kg, consider causes of water diuresis (DI, psychogenic polydipsia)
  - U_{osm} 100-300 mOsm/kg, consider causes of mixed polyuria (partial DI, CKD)
  - U_{osm} >300 mOsm/kg, consider causes of osmotic diuresis (hyperglycemia, azotemia, excess solute intake)
- water deprivation test if suspected DI, see *Diabetes Insipidus, NP12* for complete workup for diabetes insipidus

Treatment

- specific to etiology

Acute Kidney Injury

Definition

- abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
- formerly known as acute renal failure

Clinical Features

- decreased GFR
- may have weight gain and edema
- azotemia (increased BUN, Cr)
- abnormal urine volume: formally <0.5 ml/kg/h for >6 h but can manifest as anuria, oliguria, or polyuria

Table 10. Classification of Acute Kidney Injury

Stage	Serum Creatine	Urine output
1	.5-1.9 times baseline OR ≥0.3 mg/dl (>26.5 umol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatine to ≥4.0 mg/dl (≥353.6 umol/l) OR Initiation of renal replacement therapy OR In patient <18 yr, decrease in eGFR to <35 ml/min per 1.73m^2	0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

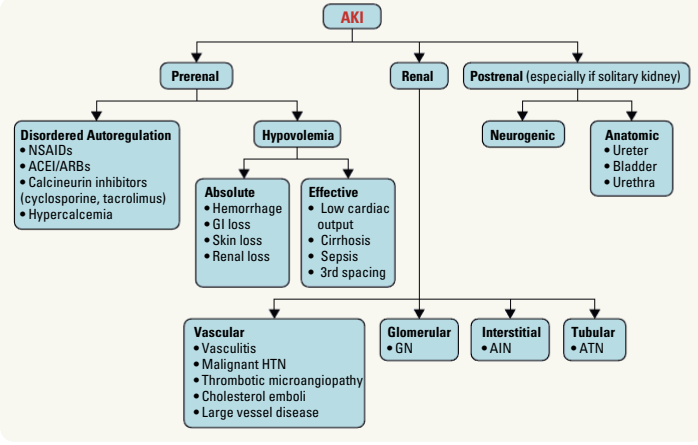

Figure 12. Approach to AKI

Investigations

- blood work: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), Ca^{2+}, PO_4^{3-}
- urine tests:
  - urine analysis: R and M, sediment, casts and crystals
  - urinary chemistry: electrolytes, osmolality, FENa
  - albumin, hemoglobin, WBCs, glucose, pH, urobilinogen, specific gravity
  - urine volume, C&S
- imaging: abdomen U/S (assess kidney size, hydronephrosis, postrenal obstruction)
- fluid challenge (e.g. fluid bolus to rule out most prerenal causes)
- indications for renal biopsy
  - diagnosis is not certain
  - prerenal azotemia or ATN is unlikely
  - oliguria persists >2-4 d
  - RPGN, signs of significant glomerular disease (proteinuria, RBC casts) despite normal kidney size/echogenicity

The 2 most common causes of acute kidney injury in hospitalized patients are prerenal azotemia (decreased perfusion) and ATN; remember that prerenal failure can lead to ATN

Differentiating Prerenal from ATN

	Prerenal	ATN
Urine Microscopy	Normal	RBC, pigmented granular casts
Urine [Na^+]	<20	>40 mEq/L
Urine osmolality	>500	<350 mOsm/kg H_2O
FENa	<1%	>2%
Plasma [Urea]/[Cr]	>20	>10-15
Response of Cr to fluid repletion	Return to baseline 1-3 d	Persistent elevation

Clues to Prerenal Etiology
- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes, oliguria
- Increased [urea] >> Increased [Cr]
- Urine [Na^+] <10-20 mmol/L
- Urine osmolality >500 mOsm/kg
- Fractional excretion of Na $^+$<1%

Clues to Renal Etiology
- Appropriate clinical context
- Urinalysis positive for casts:
  - Pigmented granular – ATN
  - WBC – AIN
  - RBC – GN
- Systemic features, anemia, thrombocytopenia, HTN, mild-moderate ECF volume overload

Clues to Postrenal Etiology
- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis
- Fractional excretion of Na $^+$>2-3 %
- Urine osmolality 250-300 mOsm/kg

Avoid NSAIDs in patients with diarrhea, heart failure, or renal failure

Renal transplant is not a therapy for AKI

Drugs Implicated in Prerenal Azotemia
Diuretics
NSAIDs
ACEI/ARBs

Treatment

1. preliminary measures
   - prerenal
     - correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEI/ARB (gently rehydrate when needed, e.g. CHF), and NSAIDs
   - renal
     - address reversible renal causes: discontinue nephrotoxic drugs, treat infection, and optimize electrolytes
     - correct ECF volume, supportive care
   - postrenal
     - consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
     - for obstruction to cause AKI, must have functional solitary kidney or obstruction affecting both kidneys
     - treat with Foley catheter insertion, indwelling bladder catheter, nephrostomy, stenting
2. treat complications
   - fluid overload
     - NaCl restriction
     - high dose loop diuretics
   - electrolyte imbalances (hyperkalemia, hyperphosphatemia, hypocalcemia, hypo/hypermagnesemia, hyperuricemia)
   - acid–base disturbances
   - adjust dosages of medications cleared by kidney (e.g. amiodarone, digoxin, cyclosporine, tacrolimus, some antibiotics, and chemotherapeutic agents)
   - dialysis
3. definitive therapy depends on etiology (e.g. corticosteroids for AIN or immunosuppression for GN)

Timing of Initiation of Renal Replacement Therapy in Acute Kidney Injury
NEJM 2020;383:240-51
Purpose: Elucidate the most effective timing for initiation of renal-replacement therapy in patients with AKI who are critically ill.
Methods Multinational RCT involving critically ill patients with AKI. Patients were randomly assigned to receive an accelerated regimen of renal-replacement therapy (initiated within 12 h after eligibility criteria were met) or a standard strategy (in which renal-replacement therapy was discouraged unless indications developed or AKI >72 h). The primary outcome was all-cause mortality at 90 d.
Results 2927 of the 3019 randomized patients were included in the final intention-to-treat analysis. The 90-day mortality was 43.9% in the accelerated group and 43.7% in the standard strategy group (RR 1.00; 95%CI 0.93 to 2.09, P=0.92). Among 90-day survivors, continued reliance on renal-replacement therapy was 10.4% in the accelerated group and 6.0% in the standard group (RR 1.74; 95% CI 1.24 to 2.43). Adverse events occurred at 23.0% in the accelerated group and 16.5% in the standard group (P<0.001).
Conclusion: Among critically ill patients with acute kidney injury, an accelerated renal-replacement strategy was not associated with lower mortality risk than standard strategy at 90 d.

Prognosis

- high morbidity and mortality in patients with sustained AKI and multi-organ failure

Parenchymal Kidney Diseases

Glomerular Diseases

HISTOLOGICAL TERMS OF GLOMERULAR CHANGES

Extent of Changes

- histological terms describing the number of glomeruli affected in a given condition:
  - diffuse: majority of glomeruli abnormal
  - focal: some glomeruli abnormal
- histological terms describing the extent to which individual glomeruli are affected in a given condition
  - global: entire glomerulus abnormal
  - segmental: only part of the glomerulus abnormal

Types of Changes

- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
- crescent formation: parietal epithelial cell proliferation (Bowman's capsule lining) and mononuclear cell infiltration form crescent-shape in Bowman's space (hallmark of inflammatory glomerulonephritis)
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane
- podocytopathy: podocyte (visceral epithelial layer) injury leading to effacement of the foot-processes that wrap around the basement membrane forming part of the filtration barrier.

CLINICAL FEATURES OF GLOMERULAR DISEASE

Important Points to Remember

- glomerular diseases have diverse clinical features including hematuria, proteinuria, HTN, edema, and decreased GFR
  - glomerular injuries may manifest as distinct syndromes depending on the pattern and extent of injury
    1. asymptomatic urinary abnormalities
       - isolated subnephrotic proteinuria
       - isolated hematuria
    2. nephritic syndrome
       - acute GN
       - rapidly progressive GN

3. nephrotic syndrome
4. ESRD

- glomerulopathies can be caused by a primary disease or can occur secondary to a systemic disease
- some glomerulopathies can present as more than one syndrome at different times

The Nephritic-Nephrotic Spectrum

- glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic (inflammation of glomeruli) and pure nephrotic syndromes (abnormal glomerular permeability) at the extremes

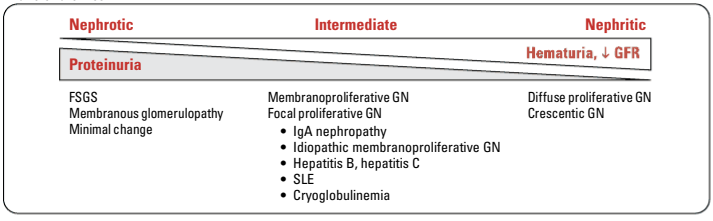

Figure 13. Spectrum of glomerular pathology

Proteinuria

- hallmark of nephrotic syndromes
- composition of normal urine protein: albumin, lower molecular proteins (such as immunoglobulin light chain), or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)
- 24 h urine protein: gold standard to assess degree of proteinuria
  - upper limit of normal daily excretion of total protein is 150 mg/d
  - upper limit of normal daily excretion of albumin is 30 mg/d, albuminuria that persists for >3 mo is considered CKD
- spot/random urine ACR: used to screen for diabetic nephropathy and proteinuric renal disease
- microalbuminuria: ACR ≥2.0 mg/mmol
  - marker of vascular endothelial function
  - an important prognostic marker for CKD (see *Diabetes Insipidus, NP12*)
  - microalbuminuria is the earliest sign of diabetic nephropathy

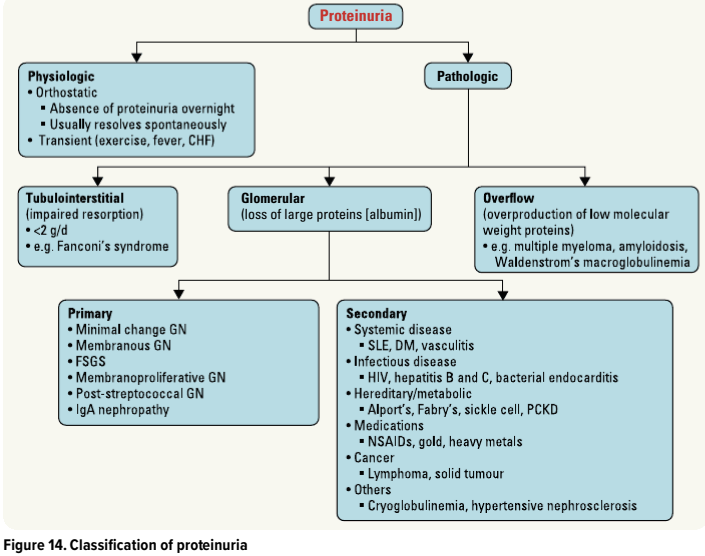

Figure 14. Classification of proteinuria

Pathologic Proteinuria

Tubulointerstitial

Normally low molecular weight proteins (<60 kDa) pass through glomerular filtration barrier and are reabsorbed in proximal tubule

Proximal tubule dysfunction causes impaired reabsorption and increased excretion of low molecular weight proteins

Albumin (>60 kDa) is not affected; thus, edema is partly secondary to salt and water retention

Glomerular

Normally, the filtration barrier is selectively permeable to size (<60 kDa) and charge (repels negative particles); thus, albumin is filtered to a very limited extent through a normal glomerulus

Damage to any component of the glomerular filtration barrier results in loss of albumin and other high molecular weight proteins; thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (possibly due to filtered proteins stimulating the action of cortical collecting duct epithelial sodium channel)

Overflow

Increased production of low molecular weight proteins which exceeds the reabsorptive capacity of the proximal tubule

Plasma cell dyscrasias produce light chain Ig (multiple myeloma, Waldenstrom's macroglobulinemia, monoclonal gammopathy of renal significance)

Table 11. Daily Excretion of Protein

Daily Excretion	Stage of Nephropathy	ACR	PCR
<150 mg total protein (and <30 mg albumin)	Normal	<2.0 mg/mmol	<15 mg/mmol
30-300 mg albumin	Microalbuminuria	>2.0 mg/mmol	
>3500 mg total protein/1.73 m ^{2}body surface area	Nephrotic range proteinuria	>220 mg/mmol	>300 mg/mmol
Variable amount of proteinuria	Can be seen with glomerular disease		
Up to 2000 mg per d	Possible tubular disease because of failure to reabsorb filtered proteins		

Investigations
- urea, creatinine, ACR, PCR
- urine R&M, C&S, urine dipstick
- further workup (if degree of proteinuria >0.5 g/d, casts, and/or hematuria)
  - CBC, glucose, electrolytes, 24 h urine protein and albumin, and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic U/S
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA (PR3), C3, C4, HBV, HCV, HIV, ASOT
- consider urology consult and possible cystoscopy if not clearly a nephrologic source for hematuria or if >50 yr of age

Glomerular Syndromes

1. ASYMPTOMATIC URINARY ABNORMALITIES

Clinical/Lab Features
- often have rapid decline in GFR, anemia, elevated inflammatory markers, ECF volume replete, or mildly overloaded
- proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
  - isolated proteinuria
    - can be postural
    - occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
  - hematuria with or without proteinuria
    - IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, frequently presents after viral upper respiratory tract infection (presents most frequently with gross hematuria)
      - more common in White and Asian populations, and in the 2nd and 3rd decades of life
      - may be associated with cirrhosis, HIV infection, celiac disease
      - mesangial deposition of IgA (more dominant) and C3 seen on immunofluorescence microscopy
      - potential treatment includes: RAAS blockers if proteinuria, steroids, and steroid sparing agents (azathioprine, cyclophosphamide, mycophenolate mofetil, and biologics such as rituximab)
    - hereditary nephritis (Alport Syndrome; Type IV collagen mutation): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/d
    - thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
    - benign recurrent hematuria: hematuria associated with febrile illness, exercise, or immunization; a diagnosis of exclusion after other possibilities are ruled out

2. NEPHRITIC SYNDROME

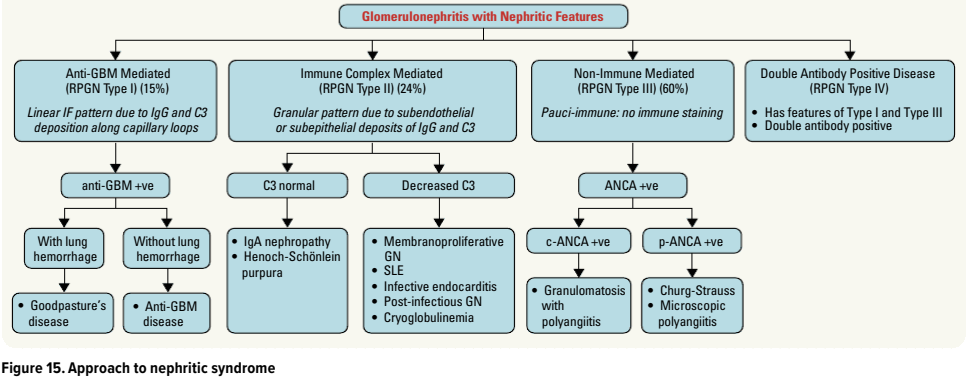

Figure 15. Approach to nephritic syndrome

Rapidly progressive GN
- a subset of nephritic syndrome in which the clinical course occurs over days
- etiology can be divided into low and normal complement levels
- frequently immune-mediated, with Ig and C3 deposits found in GBM; but may be pauci-immune and caused by an ANCA vasculitis
- nephritic syndromes usually denote proliferative glomerulonephritis.
- clinical and histopathological syndrome (e.g. (glomerular crescents on biopsy)
- any type of proliferative GN can present as RPGN
- additional etiologies seen only as RPGN: anti-GBM disease and granulomatosis with polyangiitis (GPA) (previously called Wegener's granulomatosis)
- glomerular crescents crescentic GN (identified by pathology) is frequently seen in RPGN resulting from proliferation of parietal epithelial cells and is the most aggressive form of glomerular disease

Clinical/Lab Features
- Triad of:
  - hematuria (microscopic or macroscopic), RBC casts and/or dysmorphic RBCs in urine
  - azotemia (increased Cr and urea)
  - HTN (due to salt and water retention)
- proteinuria (less than range for nephrotic syndrome, <3.5 g/1.73 m ^{2}/d)
- may have peripheral edema/puffy eyes

Treatment
- depends on etiology
- pulse steroid therapy and other immunosuppression (steroid sparing agents such as azathioprine and cyclophosphamide, mycophenolate mofetil, and biologics such as rituximab), BP control (with RAAS agents), plasma exchange, monitoring for progression to ESRD

Clinical Features
- insidious onset presenting with fatigue or edema
- oliguria (not commonly)
- hypertension

Investigations
- fibrous crescents typically present on renal histopathology
- RBC casts and/or dysmorphic RBCs in urine
- classified by immunofluorescence staining
- Type I: anti-GBM mediated (15% of cases)
- Type II: immune complex mediated (24% of cases)
- Type III: Pauci-immune (ANCA associated vasculitis) (60% of cases)
- Type IV: double antibody positive (anti-GBM and ANCA)

Treatment and Prognosis
- treatment: underlying cause if post-infectious; corticosteroids and cyclophosphamide or other cytotoxic agent and plasmapheresis to manage cases such as anti-GBM disease
- prognosis: 50% recovery with early treatment, depends on underlying cause

3. NEPHROTIC SYNDROME

Definition
- distinct constellation of clinical and laboratory features of renal disease defined by the presence of heavy proteinuria (protein excretion greater than 3.5 g/24 h), hypoalbuminemia (less than 3 g/dL), peripheral edema, and hyperlipidemia

Clinical/Lab Features
- heavy proteinuria (>3.5 g/1.73 m ^{2}/d)
- hypoalbuminemia
- edema
- hyperlipidemia (elevated LDL cholesterol due to increased liver albumin production), lipiduria (fatty casts and oval fat bodies on microscopy)
- hypercoagulable state (due to antithrombin III, Protein C, and Protein S urinary losses)
- patient may report frothy urine
- glomerular pathology on renal biopsy
- minimal change disease (or minimal lesion disease or nil disease): e.g. glomeruli appear normal on light microscopy
  - membranous glomerulopathy
  - FSGS
  - membranoproliferative GN
  - nodular glomerulosclerosis
- each can be idiopathic or secondary to a systemic disease or drug (Interferon, NSAIDs, Penicillamine)

Interventions for Renal Vasculitis in Adults
Cochrane DB Syst Rev 2015; CD003232
Purpose: To assess benefits and harms of any intervention used for the treatment of renal vasculitis in adults.
Methods: RCTs in Cochrane Kidney and Transplant Specialized Register investigating any intervention for the treatment of renal vasculitis in adults.
Conclusions: Plasma exchange was effective in patients with severe AKI secondary to vasculitis. Pulse cyclophosphamide resulted in an increased risk of relapse (compared to continuous oral) but required reduced dose. Rituximab and mycophenolate mofetil were comparable in efficacy to cyclophosphamide. Azathioprine, methotrexate and leflunomide were effective as maintenance therapy.

See Landmark Nephrology Trials table for more information on BLISS-LN which details the efficacy and safety of IV belimumab as an add-on therapy in the management of lupus nephritis.

ALMS trial is a classic LN trial that showed benefit for MMF in LN

Table 12. Nephrotic Syndrome

	Minimal Change	Membranous Glomerulopathy	Focal Segmental Glomerulosclerosis	Membranoproliferative Glomerulonephritis	Nodular Glomerulosclerosis
Secondary Causes	Hodgkin's Lymphoma (primarily) and Non-Hodgkin Lymphoma	HBV, SLE, solid tumours (lung, breast, GI)	Reflux nephropathy, HIV, HBV, obesity, sickle cell disease	HCV, malaria, SLE, leukemia, lymphoma, shunt nephritis	DM, amyloidosis
Drug Causes	NSAIDs	Gold, penicillamine	Heroin		
Therapy	Steroids	Reduce BP, ACEI, steroids, Rituximab, cytotoxic agents (cyclophosph amide), calcineurin inhibitors	Steroids, cytotoxic agents (cyclophosphamide), immunosuppressive agents (calcineurin inhibitors, cyclosporine), ACEI/ARB for proteinuria	Aspirin®, ACEI, dipyridamole (Persantine®) – controversial	Treat underlying cause

Note: the most common secondary causes are diabetes mellitus and amyloidosis

4. END STAGE RENAL DISEASE

- see *End Stage Renal Disease, NP40*

Investigations for Glomerular Disease

- blood work
  - first presentation: electrolytes, CBC, Cr, urea, albumin, fasting lipids, ACR
  - determining etiology: ESR, serum immunoelectrophoresis (for amyloidosis or multiple myeloma), C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT, VDRL, HIV, anti-GBM antibodies, serum free light chain assay, urine protein electrophoresis
- urinalysis: RBCs, WBCs, casts, protein
- 24 h urine for protein and CrCl
- radiology
  - CXR (infiltrates, CHF, pleural effusion)
  - renal U/S: with renal dopplers to rule out renal vein thrombosis
  - for Bence-Jones protein if proteinuria present
- renal pathology (light microscopy, immunofluorescence, electron microscope

SECONDARY CAUSES OF GLOMERULAR DISEASE

Amyloidosis

- nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
- presents as nephrotic range proteinuria (albuminuria) with progressive renal insufficiency
- can be primary or secondary to multiple myeloma, TB, Inflammatory diseases (e.g. rheumatoid arthritis), or malignancy

Systemic Lupus Erythematosus

- see Rheumatology, RH11
- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- GN caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complements (C3 and C4),levels are usually low during periods of active renal disease, Anti-dsDNA levels are high
- children and males with SLE are more likely to develop

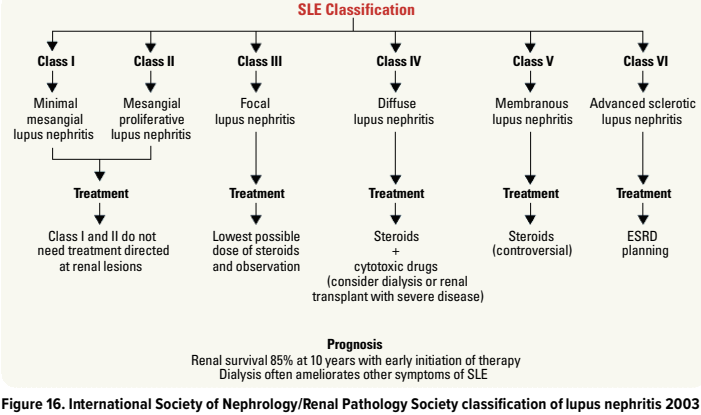

Figure 16. International Society of Nephrology/Renal Pathology Society classification of lupus nephritis 2003

EULAR Recommendations for the Management of Systemic Lupus Erythematosus (SLE)
Ann Rheum Dis 2008;67:195-205
Lupus Nephritis Recommendations
Monitoring: Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) have limited ability to predict response to treatment and may be used only as supplemental information.
Treatment: In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and has a more favourable toxicity profile. If failure to respond by 6 mo consider intensifying therapy. Flares following remission are not uncommon and require diligent follow-up.
End-Stage Renal Disease: Dialysis and transplantation in SLE have long-term patient and graft-survival rates comparable with those observed in non-diabetic non-SLE patients. Transplantation is the method of choice.

IgA Vasculitis (Henoch-Schönlein Purpura)
- systemic IgA vasculitis, tissue deposition of IgA1-dominant immune complexes affecting mostly small vessels
- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia, and fever
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

ANCA-Associated Vasculitis
- multi system or renal limited disease
- c-ANCA (anti-Proteinase 3 (PR3)) most commonly associated with the clinical picture of granulomatosis with polyangiitis
- p-ANCA (anti-Myeloperoxidase (MPO)) most commonly associated with the clinical picture of microscopic polyangiitis
- focal segmental necrotizing RPGN (crescents) with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treatment typically involves Steroids and cyclophosphamide/Rituximab
- plasmapheresis is indicated in severe renal disease and/ or pulmonary hemmorhage.

Cryoglobulinemic Vasculitis
- cryoglobulins: monoclonal IgM (Type I) and polyclonal IgG (Type II and Type III)which precipitate at reduced temperatures, deposit in walls of small vessels
- presents as purpura, fever, Raynaud's phenomenon, and arthralgias, AKI
- at least 50% of patients have HCV
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treatment: antiviral therapy for HCV, plasmapheresis, steroids, cyclophosphamide, myeloma therapy
- overall prognosis: 75% renal recovery

Shunt Nephritis
- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- commonly caused by *S. epidermidis*
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients
- treat by removing shunt and administering appropriate antibiotics; can consider a ventriculoperitoneal shunt

HIV-Associated Renal Disease
1. direct nephrotoxic effect of HIV infection, anti-retroviral drugs (e.g. tenofovir, indinavir), and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy

- histology: focal and segmental glomerular collapse with mesangial sclerosis; "collapsing FSGS"
  - tubular cystic dilation and tubulo-reticular inclusions
  - clinical features: predominant in African American men, heavy proteinuria, progressive renal insufficiency (Apo-L-1 risk genotypes)
  - prognosis: kidney failure within 1 yr without treatment
  - therapy: short-term, high dose steroids, ACEI, HAART

Infective Endocarditis
- manifests as mild form of acute nephritic syndrome with decreased serum complement
- *S. aureus* is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

Hepatitis B
- can result in membranous nephropathy, membranoproliferative GN, and polyarteritis nodosa

Hepatitis C
- can result in membranous nephropathy, membranoproliferative GN, and cryoglobulinemia

Syphilis
- can result in membranous GN

Tubulointerstitial Disease

TUBULOINTERSTITIAL NEPHRITIS

Definition
- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

Signs and Symptoms
- manifestation of disease depends on site of tubule affected
  1. proximal tubule (e.g. multiple myeloma, heavy metals, genetic diseases such as Dent's disease or Lowes disease)
     - Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, and hyperuricosuria
     - proximal RTA (decreased bicarbonate absorption): Type II RTA
  2. distal tubule (e.g. amyloidosis, obstruction)
     - distal RTA (decreased hydrogen secretion, usually hypokalemic): Type I RTA
     - Na $^{+}$-wasting nephropathy
     - ± hyperkalemia leading to Type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
  3. collecting duct (e.g. sickle cell anemia, analgesics, primary ciliary dyskinesia)
     - urinary concentrating defect leading to mild nephrogenic DI
     - polyuria

IgA nephropathy is the most common type of primary glomerular disease worldwide

Features of Nephritic Syndrome

PHAROH
Proteinuria
Hematuria
Azotemia
RBC casts
Oliguria
HTN

Presentation of Nephrotic Syndrome

HELP
Hypoalbuminemia
Edema
Lipid abnormalities
Proteinuria

1. ACUTE TUBULOINTERSTITIAL NEPHRITIS

Definition
- rapid (days to weeks) decline in renal function
- 10-20% of all AKI

Etiology
- hypersensitivity
  1. antibiotics: β-lactams, sulfonamides, rifampin, quinolones, cephalosporins
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
- infections
  - bacterial pyelonephritis, *Streptococcus*, brucellosis, *Legionella*, CMV, EBV, toxoplasmosis, leptospirosis, HIV, *Mycoplasma*
- immune
  - SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia (Type III)
- idiopathic (renal-ocular syndrome – acute TIN plus uveitis)

Pathophysiology
- acute inflammatory cell infiltrates into renal interstitium

Clinical Features
- AKI
- if hypersensitivity reaction (common with antibiotics): may see fever, eosinophilia, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
- if pyelonephritis: flank pain and costovertebral angle tenderness
- if drug reaction, AKI usually occurs 7-10 d after exposure
- other signs and symptoms based on underlying etiology
- HTN and edema are uncommon

Findings
- urine
  - mild, non-nephrotic range proteinuria and microscopic hematuria
  - sterile pyuria, WBC casts
  - eosinophils if AIN
- blood work
  - increased Cr and urea
  - eosinophilia if drug reaction (high negative predictive value, common in β-lactam reactions)
  - normal AG metabolic acidosis (RTA)
  - hypophosphatemia, hypo- OR hyperkalemia, hyponatremia
- gallium scan often shows intense signal due to inflammatory infiltrate
- renal biopsy definitive – shows interstitial infiltrates and edema on biopsy

Treatment
- treat underlying cause (e.g. stop offending medications, treat infection with antibiotics if present i.e. pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

Prognosis
- recovery within 2 wk if underlying insult can be eliminated
- the longer the patient is in renal failure, the less likely they will have a full renal recovery

2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Definition
- characterized by slowly progressive renal failure, moderate proteinuria, and signs of abnormal tubule function

Etiology
- persistence or progression of acute TIN
  - may also involve concurrent glomerular manifestations
- urinary tract obstruction: most important cause of chronic TIN (tumours, stones, bladder outlet obstruction, vesicoureteral reflux)
- chronic pyelonephritis due to vesicoureteral reflux or UTI with obstruction
- nephrotoxins
  - exogenous
    - analgesics: NSAIDs (common), acetaminophen
    - cisplatin, lithium, cyclosporine, tacrolimus
    - heavy metals (lead, cadmium, copper, lithium, mercury, arsenic)
    - Chinese herbs (aristolochic acid)
  - endogenous
    - hypercalcemia, hypokalemia, oxalate, uric acid
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma, lymphoma
- granulomatous: TB, sarcoidosis, granulomatosis with polyangiitis, inflammatory bowel disease
- immune: SLE, Sjögren's, cryoglobulinemia, anti-GBM disease, amyloidosis, renal graft rejection, vasculitis
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

Pathophysiology
- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

Signs and Symptoms
- dependent on underlying etiology

Findings
- non-AG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi's syndrome
- progressive renal failure with azotemia and uremia
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- U/S: shrunken kidneys with irregular contours (differentiates acute from chronic etiology)

Treatment
- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders (Ca^{2+}, PO_4^{3-}) and anemia

3. ACUTE TUBULAR NECROSIS

Definition
- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis
Ann Intern Med 2016;164(6):406-416
Purpose: To evaluate the comparative effectiveness of interventions to reduce contrast-induced nephropathy in adults receiving contrast media.
Methods: Meta-analysis of RCTs N-acetylcysteine, sodium bicarbonate, statins, or ascorbic acid that used IV or intra-arterial contrast media.
Results: Low dose N-acetylcysteine+IV saline vs. IV saline (RR 0.75, 95% CI 0.63-0.89). N-acetylcysteine+IV saline vs. IV saline (RR 0.69, 95% CI 0.58-0.84). Statins+N-acetylcysteine+IV saline vs. N-acetylcysteine+IV saline (RR 0.52, 95% CI 0.29-0.93). Clinically important, but not statistically significant, reductions were observed in sodium bicarbonate vs. IV saline, statins+IV saline vs. IV saline, and ascorbic acid vs. IV saline.
Conclusions: Greatest reduction in contrast-induced nephropathy was seen with N-acetylcysteine plus IV saline and statins plus N-acetylcysteine plus IV saline.

Etiology

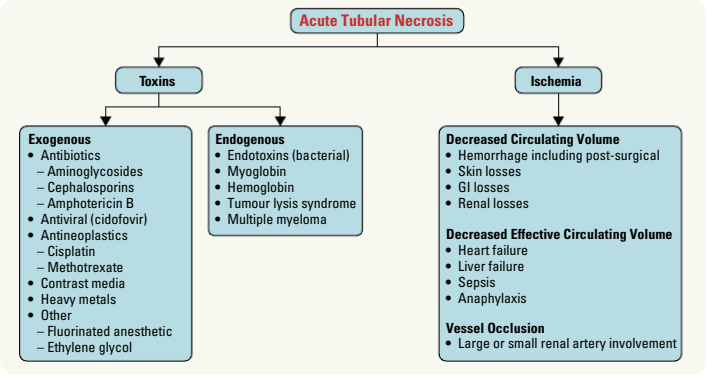

Figure 17. Etiology of ATN

Clinical Features

- typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
  - pre-renal AKI can eventually progress to ATN
  - consists of three phases:
    - oliguric: decreased urinary output from renal damage, azotemia, and uremia; lasts 10-14 d
    - diuretic: urinary output >500 mL/day (result of retained water, salt, and solutes during oliguric phase) and tubular cell damage
    - recovery: tubular function recovers
- physical exam may show signs of true or effective ECF volume depletion
- most common cause of non-prerenal AKI in hospitalized patients
- urine: high FE_{Na} (>2%), pigmented-granular casts

Risk Factors

- pre-existing CKD, pre-existing cardiovascular disease, ECF volume depletion, multiple renal insults

Complications

- hyperkalemia: can occur rapidly and cause serious arrhythmias
- metabolic acidosis, decreased Ca^{2+}, increased PO_4^{3-}, hypoalbuminemia

Investigations

- blood work: CBC, electrolytes, Cr, urea, Ca^{2+}, PO_4^{3-}, blood gasses
- urine: R&M, electrolytes, osmolality, microscopic urinalysis searching for heme granular/muddy brown casts
- ECG (monitor for arrhythmias due to hyperkalemia)
- abdominal U/S
- rule out other causes of prerenal/postrenal azotemia and intrinsic AKI (GN, AIN, vasculitis)
  - IV fluid challenge will not increase urine output or normalize serum creatinine in ATN, helps to differentiate ATN from pre-renal AKI
  - if diagnosis is uncertain, biopsy

Treatment

- largely supportive once underlying problem is corrected
- dialysis if indicated (refractory volume overload, metabolic acidosis, hyperkalemia, uremic encephalopathy or pericarditis)
- no benefit found for early start dialysis in critically ill patients

Prevention

- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast:
  - isotonic saline
  - avoid giving diuretics, NSAIDS, ACEI, cyclosporine on morning of procedure if possible
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency
- use low dose non-ionic, iso- or low-osmolal contrast agents

Vascular Diseases of the Kidney

LARGE VESSEL DISEASE

Table 13. Summary of Vascular Diseases

Large Vessel Disease	Medium Vessel Disease	Small Vessel Disease
Acute renal artery occlusion (infarct)	Kawasaki disease	Hypertensive nephrosclerosis
Renal artery stenosis (ischemia)	Polyarteritis nodosa	Atheroembolic renal disease
Renal vein thrombosis	ANCA-associated vasculitis	Thrombotic microangiopathy
		Scleroderma
		Calcineurin inhibitor nephropathy
		HUS
		ANCA-associated vasculitis

1. RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)

- important, potentially reversible cause of renal failure

Etiology

- abdominal trauma, surgery, embolism, vasculitis, extrarenal compression, hypercoagulable state, aortic dissection
- kidney transplant recipients more vulnerable

Signs and Symptoms (depend on presence of collateral circulation)

- fever, N/V, flank pain
- leukocytosis, elevated AST, ALP
- marked elevated LDH (LDH >4x upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
- acute onset HTN (activation of RAAS) or sudden worsening of long-standing HTN
- renal dysfunction, e.g. elevated Cr (if bilateral, or solitary functioning kidney)

Investigations

- renal arteriography (more reliable but risk of atheroembolic renal disease)
- contrast-enhanced CT or MR angiography, duplex Doppler studies (operator dependent)

Treatment

- prompt localization of occlusion and restoration of blood flow
- anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
- medical therapy in the long-term to reduce risk (e.g. antihypertensives)

2. ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)

- chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
- significant cause of ESRD: 15% in patients >50 yr (higher prevalence if significant vascular disease)
- usually associated with large vessel disease elsewhere
- causes of renal artery stenosis
  - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males >55 yr, smokers
  - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset <30 yr)
- when there is decreased RBF, GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the FF (GFR/RBF)
- most common cause of secondary HTN ("renovascular HTN"), 1-2% of all hypertensive patients
  - etiology
    - decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
    - increased angiotensin raises blood pressure in two ways
    1. causes generalized arteriolar constriction
    2. release of aldosterone increases Na^+ and water retention
      - elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN

Risk Factors

- age >50 yr
- smoking
- other atherosclerotic disease (dyslipidemia, DM, diffuse atherosclerosis)

Signs and Symptoms

- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

Treatment of Hypertension in Association with Renovascular Disease
Can J Cardiol 2017;33(5):557-576
Guidelines:
1. Recommend medical management as renal angioplasty and stenting offers no benefit over optimal medical therapy alone
2. In patients with uncontrolled HTN resistant to maximally tolerated pharmacotherapy, progressive renal function loss and acute pulmonary edema, renal artery angioplasty and stenting for atherosclerotic hemodynamically significant stenosis could be considered
3. Patients with confirmed renal fibromuscular dysplasia should be referred to HTN specialist and considered for revascularization

Investigations
- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (e.g. captopril renal scan)
- renal arteriography (gold standard, but risk of contrast nephropathy)

Treatment
- treatment of renal artery stenosis is performed for select cases of blood pressure control, treatment of heart failure, pulmonary edema, and prevention of nephropathy
- medical therapy includes potential use of ACEI, statins, and platelet inhibitors
- revascularization using stenting is performed to treat or prevent development of ischemic nephropathy, although there is debate surrounding its efficacy
- surgical bypass or reconstruction is an option but benefit over angioplasty is debated

Stenting and Medical Therapy for Atherosclerotic Renal Artery Stenosis
NEJM 2014;370:13-22
Study: Multicentre, unblinded RCT, median follow-up of 43 mo.
Patients: 947 patients with atherosclerotic renal-artery stenosis who also have significant systolic HTN or CKD.
Intervention: 947 patients with atherosclerotic renal-artery stenosis who also have significant systolic HTN or CKD.
Intervention: Percutaneous revascularization (stenting) with medical therapy (statins, ARB, calcium channel blockers, HCTZ, and BP control) vs. medical therapy alone.
Outcomes: Occurrence of adverse CV or renal event (composite of death from CV or renal cause, MI, stroke, hospitalization for CHF, progressive renal insufficiency, or need for renal replacement therapy) and all-cause mortality.
Outcomes: Occurrence of adverse CV or renal event (composite of death from CV or renal cause, MI, stroke, hospitalization for CHF, progressive renal insufficiency, or need for renal replacement therapy) and all-cause mortality.
Results: No significant difference in primary composite endpoint between participants who received stenting or those on medical therapy alone. No significant differences between the treatment groups in the rates of the individual components of the primary endpoint or in all-cause mortality..
Conclusion: Renal artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal artery stenosis and HTN or CKD.

3. RENAL VEIN THROMBOSIS

Etiology
- endothelial damage: blunt trauma, tumour infiltration (e.g. RCC), vasculitis, renal transplant, and acute rejection
- stasis: severe volume loss (i.e. GI fluid loss, hemorrhage, dehydration), renal vein compression
- hypercoagulability: nephrotic syndrome, sepsis, oral contraceptives, disseminated malignancy, intrinsic hypercoagulability, sickle cell disease
- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical features determined by rapidity of occlusion and formation of collateral circulation

Signs and Symptoms
- acute: N/V, flank pain, hematuria, elevated plasma LDH, ± rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria, and/or tubule dysfunction

Investigations
- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

Treatment
- anticoagulation therapy to aid in recanalisation, improve renal function, and reduce risk of thromboembolism. Initial treatment using IV heparin, followed by warfarin (target INR 2.5) within 3-10 d continued for minimum 1 yr
- certain cases are suitable for thrombectomy or thrombolysis (local or systemic). Commonly used agents include streptokinase, urokinase, and tissue plasminogen activators

MEDIUM VESSEL DISEASE

1. KAWASAKI DISEASE
- see Pediatrics, P99

2. POLYARTERITIS NODOSA
- see Rheumatology, RH21
- kidneys most commonly involved organ
- heterogenous impact on renal function
- pathologically can cause glomerular ischemia which manifests as mild proteinuria and hypertension

SMALL VESSEL DISEASE

1. HYPERTENSIVE NEPHROSCLEROSIS
- see *Hypertension, NP38*

2. ATHEROEMBOLIC RENAL DISEASE
- progressive renal insufficiency due to embolic obstruction of small- and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
- anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
- investigations
  - eosinophilia, eosinophiluria, and hypocomplementemia
  - renal biopsy: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small-/medium-sized vessels

- treatment
  - no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
- prognosis: poor overall, at least one third will develop ESRD

3. THROMBOTIC MICROANGIOPATHY

- see Hematology, H23
- etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia, drug-induced, complement mediated, metabolism-mediated, and coagulation-mediated
- the enzyme ADAMTS13 is reduced in TTP, and ADAMTS13 autoantibodies are useful for diagnosing TTP
- events leading to HUS often begin with the ingestion of Shiga toxin-producing E. coli
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
- treatment
  - depends on cause
  - supportive therapy
  - TTP-HUS: plasma exchange, corticosteroids
  - eculizumab (monoclonal antibody against complement C5) for Complement mediated HUS (previously known as atypical HUS)
- avoid platelet transfusions and ASA

4. CALCINEURIN INHIBITOR NEPHROPATHY

- secondary to the use of cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplants (e.g. heart)
- acute: due to afferent and efferent arteriolar vasoconstriction leading to decreased GFR (tubular vacuolization)
  - prerenal azotemia
  - treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
- chronic: result of obliterative arteriolopathy causing interstitial nephritis and CKD (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation (ELITE-Symphony Trial)
NEJM 2007;257:2562-2575
Study: Multicentre, RCT with 12 mo follow-up.
Patients: 1645 patients scheduled to receive a single organ kidney transplant.
Intervention: Mycophenolate mofetil, corticosteroids, and either: 1) standard dose cyclosporine; 2) low dose cyclosporine with daclizumab induction; 3) low dose tacrolimus with daclizumab induction; 4) low dose sirolimus with daclizumab induction.
Primary Outcome: Estimated Cockcroft-Gault GFR 12 mo after transplantation.
Results: The tacrolimus arm showed significantly higher eGFR at 12 mo compared to all other arms (65.4 mL/min vs. 57.1, 59.4, 56.7 for arms 1, 2, 4 respectively, P≤0.001). The tacrolimus arm also showed decreased rates of acute rejection at 6 mo and 12 mo vs. all arms (P<0.001), improved allograft survival against standard dose cyclosporine and sirolimus, and decreased treatment failure against all other arms. There was no difference in overall patient survival between groups. Sirolimus had the highest incidence of lymphoceles, delayed wound healing, and serious adverse events; tacrolimus had significantly higher rates of new-onset DM; and cyclosporine regimes had the lowest incidence of diarrhea but highest opportunistic infection rates.
Conclusion: Immunosuppression regiments using low dose tacrolimus and daclizumab induction decrease nephrotoxicity while maintaining therapeutic immunosuppression in renal transplant patients.

Analgesic Nephropathies

1. Vasomotor AKI

- clinically: develop prerenal azotemia days after NSAID initiations
- normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
- NSAIDs act by inhibiting cyclooxygenase activity, thereby preventing prostaglandin synthesis and causing renal ischemia
- more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
- treatment: discontinue NSAID, dialysis rarely needed

2. Acute Interstitial Nephritis

- caused by fenoprofen (60%), ibuprofen, naproxen
- may be associated with minimal change glomerulopathy and nephrotic range proteinuria
- resolves eventually with discontinuation of NSAID, may require interval dialysis
- short-term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

3. Chronic Interstitial Nephritis

- due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
- seen in patients who also have emotional stress, psychiatric symptoms, and GI disturbance
- papillary necrosis occurs
  - gross hematuria, flank pain, declining renal function
  - calyceal filling defect seen with IVP – "ring sign"
- increased risk of transitional cell carcinoma of renal pelvis
- good prognosis if discontinue analgesics

4. Acute Tubular Necrosis

- can be caused by acetaminophen
  - incidence of renal dysfunction is related to the severity of acetaminophen ingestion
- vascular endothelial damage can also occur
- both direct toxicity and ischemia contribute to the tubular damage
- renal function spontaneously returns to baseline within 1-4 wk
- dialysis may be required during the acute episode of ingestion

5. Other Effects of NSAIDs
- sodium retention (2° to reduced GFR)
- hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
- excess water retention (2° to loss of antagonistic effect of prostaglandins on ADH)

Systemic Disease with Renal Manifestation

Diabetes

- diabetic nephropathy is a slow, progressive increase in albuminuria, followed by a decrease in eGFR <60 later in disease course
- key risk factors include:
  - long duration of diabetes
  - non-optimal glycemic control, blood pressure, and plasma lipid control
  - obesity
  - cigarette smoking
- most common cause of end-stage renal failure in North America
- 50% of patients with diabetes will develop nephropathy
- greater burden in Indigenous communities
  - in Indigenous youth diagnosed with diabetes before age 20, risk of developing ESRD was 2.59 times higher than non-Indigenous people with diabetes
  - 55.1% of Indigenous individuals diagnosed with diabetes had chronic kidney disease
- at diagnosis up to 30% of patients with type 2 DM have albuminuria (75% A2 albuminuria, 25% overt nephropathy)
- A2 albuminuria (30 -300 mg/d) is a risk factor for progression to overt nephropathy and cardiovascular disease
- once A3 albuminuria (>300 mg/d) is established, renal function declines, 50% of patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially type 1 DM) and/or neuropathy (especially type 2 DM)
- indication of possible non-diabetic cause of renal disease in patients with DM
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of other systemic disease
  - time course of kidney disease progression disproportionate with length of diabetes; i.e. renal disease in a patient with short duration of DM; rapidly rising Cr.
  - family history of non-diabetic renal disease (e.g. PKD, Alport's)

DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD; the others are amyloidosis, HIV nephropathy, PKD, and multiple myeloma

Abnormal Urine ACR Values from 2018 Diabetes Canada CPG
≥2.0 mg/mmol in males and females

ACEI can cause hyperkalemia; therefore, be sure to watch serum K^+, especially if patient has DM and renal insufficiency

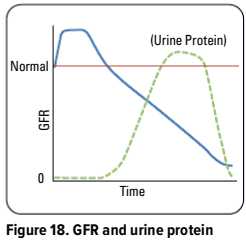

Figure 18. GFR and urine protein over time in DM

DIABETIC RENAL COMPLICATIONS

1. Progressive Glomerulosclerosis
- classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
- more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix

Table 14. Stages of Diabetic Progressive Glomerulosclerosis

	Stage 1	Stage 2	Stage 3	Stage 4
Clinical	↑GFR (120-150%) – compensatory hyperfiltration	Detectable A2 albuminuria (30-300 mg/24 h)	A3 albuminuria (>300 mg/24 h)	
		ACR 2.0-20 mg/mmol (18-180 mg/d)	ACR >20 mg/mmol, (>180 mg/d)	↓ GFR
			Proteinuria (positive urine dipstick)	
			Normal GFR	
Pathological	± slightly ↑ mesangial matrix		↑↑↑ mesangial matrix	Sclerosed glomeruli
				<20% glomerular filtration surface area present

Protein Restriction for Diabetic Renal Disease
Cochrane DB Syst Rev 2007;4:CD002181
Purpose: To review the effects of dietary protein restriction on the progression of diabetic nephropathy.
Study Selection: RCTs and before and after studies of the effects of restricted protein diet on renal function in subjects with DM. 12 studies were reviewed.
Results: The risk of ESRD or death was lower in patients on low-protein diet. In patients with type 1 DM no effect on GFR was noted in the low-protein diet group.

See Landmark Nephrology Trials table for more information on ONTARGET, which details the efficacy of ACEI/ARB combination therapy on renal outcomes in patients with atherosclerotic vascular disease or T2DM. ± slightly ↑ mesangial matrix

2. Accelerated Atherosclerosis
- common
- leads to decreased GFR
- may increase angiotensin II production resulting in increased BP
- increased risk of ATN secondary to contrast media

See Landmark Nephrology Trials table for more information on CREDENCE which details the efficacy of canagliflozin (SGLT2 inhibitor) on renal outcomes in patients with T2DM an diabetic nephropathy

3. Autonomic Neuropathy
- causes atonic bladder, which leads to functional obstruction and urinary retention
- residual urine promotes infection
- obstructive nephropathy

4. Papillary Necrosis
- type 1 DM susceptible to ischemic necrosis of medullary papillae
- sloughed papillae may obstruct ureter
- can present as renal colic or with obstructive features ± hydronephrosis

Priorities in the Management of Patients with DM
1. vascular protection for all patients with DM
   - ACEI, antiplatelet therapy (as indicated)
   - BP control, glycemic control, lifestyle modification, lipid control
   - SGLT2 inhibition (i.e. canagliflozin, dapagliflozin, and empagliflozin) provides renoprotection independent of glycemic effects
   - mineralocorticoid receptor antagonists (i.e. finerenone) provide renoprotection of top of RAAS blockade
2. optimization of BP in patients who are hypertensive
   - treat according to HTN guidelines (current target <130/80)
3. renal protection for DM patients with nephropathy (even in absence of HTN)
   - 1st line: ACEI or ARB
   - 2nd line agents:dihydropyridine calcium channel blockers
   - combination of ACEI and ARB not recommended
4. smoking cessation

- check serum Cr and K^+levels within 1 wk of initiating ACEI or ARB and at time of acute illness
- serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
- if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
- consider holding ACEI, ARB, and/or diuretic with acute illness and in women before pregnancy
- consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive loss of kidney function, inability to achieve BP targets, or inability to stay on ACEI or ARB

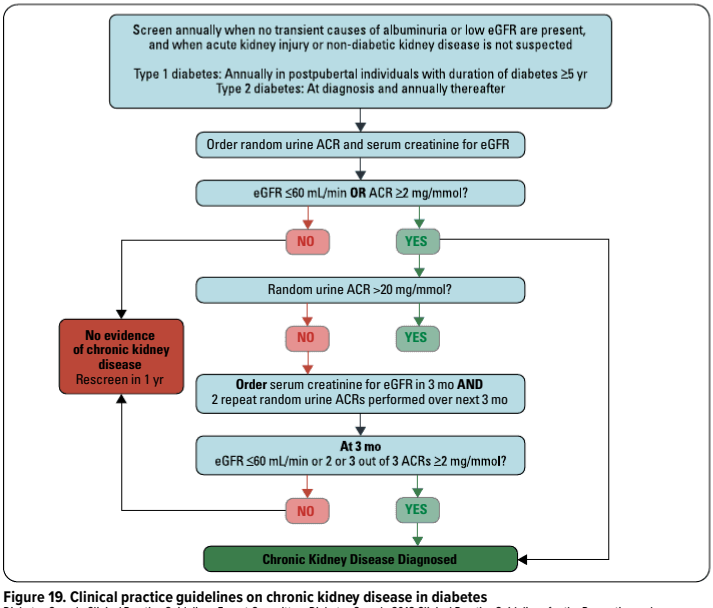
Screen annually when no transient causes of albuminuria or low eGFR are present, and when acute kidney injury or non-diabetic kidney disease is not suspected
Type 1 diabetes: Annually in postpubertal individuals with duration of diabetes ≥5 yr
Type 2 diabetes: At diagnosis and annually thereafter
Order random urine ACR and serum creatinine for eGFR
eGFR ≤60 mL/min OR ACR ≥2 mg/mmol?
NO
YES
Random urine ACR >20 mg/mmol?
NO
YES
No evidence of chronic kidney disease
Rescreen in 1 yr
Order serum creatinine for eGFR in 3 mo AND
2 repeat random urine ACRs performed over next 3 mo
At 3 mo
eGFR ≤60 mL/min or 2 or 3 out of 3 ACRs ≥2 mg/mmol?
NO
YES
Chronic Kidney Disease Diagnosed

Figure 19. Clinical practice guidelines on chronic kidney disease in diabetes
Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2018;42(Suppl 1):S1-S325

Scleroderma

- see Rheumatology, RH14
- 50% of patients with scleroderma have renal involvement (mild proteinuria, high Cr, HTN)
- renal involvement usually occurs early in the course of illness
- histology: media thickened, "onion skin" hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli, TMA
- 10-15% of scleroderma patients have a "scleroderma renal crisis" (occurs in first few years of disease, associated with prednisone dose ≥15mg / d and cyclosporine use): malignant HTN, ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- treatment: BP control with ACEI slows progression of renal disease

Multiple Myeloma

- see Hematology, H51
- malignant proliferation of plasma cells in the bone marrow with the production of monoclonal immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms
  - hypercalcemia
  - light chain cast nephropathy or "myeloma kidney"
  - hyperuricemia
  - infection
  - primary (AL) amyloidosis and secondary (AA) amyloidosis: predominantly manifesting as proteinuria with or without nephrotic syndrome
  - monoclonal Ig deposition disease
  - diffuse tubular obstruction
- light chain cast nephropathy
  - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
  - proteinuria and renal insufficiency can progress rapidly to kidney failure
- monoclonal immunoglobulin deposition disease
  - deposits of monoclonal Ig in kidney, liver, heart, and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy) or MPGN
- fibrillary/ immunotactoid Glomerulonephritis
- cryoglobulinemia (Type I) (see *NP27*)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

Malignancy

- cancer can have many different renal manifestations
- kidney transplantation cannot be performed if there is a malignancy. Nephrology considerations for malignant presentations include:
  - solid tumours: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
  - renal cell carcinoma
  - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction, hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, elevated LDH, and lactic acidosis
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumours/metastases: postrenal failure secondary to obstruction
  - primary (AL) amyloidosis and secondary (AA) amyloidosis: predominantly manifesting as proteinuria with or without nephrotic syndrome
  - radiotherapy (radiation nephritis)

Chronic Kidney Disease

Definition

- progressive abnormalities of kidney function for ≥3 mo, with either
  - GFR <60 mL/min/1.73 m ^{2}; or
  - markers of kidney damage, including:
    - hematuria, proteinuria, or anatomic abnormalities

Clinical Features

- many patients are asymptomatic till alte stages of disease
- cardiovascular: HTN, CHF (volume overload, HTN, and anemia), pericarditis (uremia)
- GI: N/V, anorexia, dysgeusia (GI symptoms typically only manifest in CKD G5)

2016 CCS Guidelines for the Management of Dyslipidemia for the Prevention of CVD in the Adult – Chronic Kidney Disease
Can J Cardiology 2016;32:1263-82
Recommendations:
Adults ≥50 yr with CKD (GFR <60 mL/min/1.73 m²) should receive treatment with a statin or a statin/ezetimibe combination.
Initiation of lipid-lowering therapy is not recommended for adults with dialysis-dependent CKD however, if already receiving it at the time of dialysis initiation, it should be continued.
Statin therapy should be used in adults with kidney transplantation.

Incidence of Etiologies of CKD	
DM	42.9%
HTN	26.4%
Glomerulonephritis	9.9%
Other/Unknown	7.7%
Interstitial nephritis/ Pyelonephritis	4.0%
Cystic/Hereditary/Congenital	3.1%
Secondary GN/Vasculitis	2.4%

- neurologic: lethargy, confusion, neuropathy, seizures, asterixis, hyperreflexia, restless leg syndrome, encephalopathy (uremia)
- hematologic: normocytic normochromic anemia (reduced EPO), bleeding due to platelet dysfunction (uremia)
- endocrine/metabolic: Ca^{2+}, PO_4^{3-} disturbances, hyperphosphatemia, hypocalcaemia, secondary hyperparathyroidism, reduced renal production of 1,25-dihydroxy vitamin D, osteopenia/osteoporosis
- sexual/reproductive: hypothalamic pituitary disturbances, infertility
- pruritus: multifactorial etiology

Table 15. Stages of CKD (KDIGO, 2013)

			Persistent Albuminuria Categories		
		GFR (mL/min/1.73 m²)	A1 <30 mg/g <3 mg/mmol	A2 30-300 mg/g 3-30 mg/mmol	A3 >300 mg/g >30 mg/mmol
GFR Categories (mL/min/1.73 m²)	G1	≥90	1 if CKD	1	2
	G2	60-89	1 if CKD	1	2
	G3a	45-59	1	2	3
	G3b	30-44	2	3	3
	G4	15-29	3	3	4+
	G5	<15 (kidney failure)	4+	4+	4+

The numbers in the boxes are a reflection of the risk of progression and are a guide to the frequency of monitoring/year
"D" is added to G5 for patients requiring dialysis
Classification is based on cause, GFR, and amount of albuminuria
Rate of progression and risk of complications are determined by the cause of CKD

Management of Complications of CKD

Management of Chronic Kidney Disease

- diet
  - preventing HTN and volume overload
  - low-protein diet with adequate caloric intake in order to limit endogenous protein catabolism. Not recommended in children as protein is needed for growth. Literature is conflicted regarding use of protein restriction in certain other populations
  - Na +restriction (<2 g/d) if HTN, CHF, or oliguria are present
  - K +restriction (40-60 mmol/d), phosphate (1 g/d) for hyperkalemia and hyperphosphatemia respectively," magnesium (avoid antacids; preventing uremia and potentially delaying decline in GFR) intake
- medical
  - adjust dosages of renally excreted medications
  - HTN: target BP now as per the most recent CSN guideline: systolic <120
  - ACEI/ARB (target SBP 120 mmHg) in patients without kidney transplant; CCB/ARB (target BP 130/80 mmHg) in patients receiving kidney transplant
  - dyslipidemia: statins (target LDL <2 mmol/L)
  - calcium and phosphate disorders
    - consider vitamin D and calcitriol (1,25-dihydroxy-vitamin D) for secondary hyperparathyroidism
    - calcium carbonate as a phosphate binder for hyperphosphatemia
    - sevelamer or lanthanum salts as a phosphate binder if both hypercalcemic and hyperphosphatemic
    - parathyroidectomy or cinacalcet for tertiary hyperparathyroidism (sensitizes parathyroid to Ca^{2+}, decreasing PTH)
  - metabolic acidosis: sodium bicarbonate
  - anemia: IV vs PO iron if TSAT ≤ 20% or ferritin ≤ 200 and an increase in Hb/decrease in ESA is desired; avoid IV in active systemic infections. Erythropoietin-Stimulant Agent (ESA) initiation if Hb <100, with target 95-110. Epoetin-alfa, or darbepoetin are erythropoesis stimulating agents. Contraindications: active malignancy, history of stroke, history of malignancy
  - platelet dysfunction: DDAVP if patient has clinical bleeding or invasive procedures
  - dialysis (see Indications for Dialysis in *Chronic Kidney Disease, NP41*)
  - renal transplantation for end stage kidney disease

Prevention of Progression

- as above
- control of HTN, DM (HbA1c <7%), cardiovascular risk factors (e.g. smoking cessation, physical activity, weight loss)
- avoid nephrotoxins such as NSAIDs, COX2 inhibitors, IV contrast in patients with eGFR <60 mL/min/1.73 m²
- address reversible causes of AKI

Management of Complications of CKD

NEPHRON
Nephrotoxins: avoid nephrotoxic drugs (ASA, gentamicin) and adjust doses of renally excreted medications
HTN
RBCs: manage anemia with erythropoietin
Osteodystrophy: give calcium between meals (to increase Ca^{2+}) and calcium with meals (to bind and decrease PO_4^{3-})
Nitrogen diet
Electrolytes: monitor K+
pH: metabolic acidosis

Effects of Lowering LDL Cholesterol with Simvastatin and Ezetimibe in Patients with Chronic Kidney Disease
Lancet 2011;377:2181-2192
Purpose: To assess the efficacy and safety of the combination of simvastatin and ezetimibe in patients with moderate to severe CKD.
Study: Randomized, double-blind trial with 9270 patients with CKD with no known history of myocardial infarction or coronary vascularization. Patients were randomized to simvastatin 20 mg plus ezetimibe 10 mg daily vs. matching placebo.
Primary Outcome: First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure).
Results: The simvastatin plus ezetimibe group was associated with an average LDL cholesterol difference of 0.85 mmol/L during a median follow-up of 4.9 yr. There was a 17% proportional reduction in major atherosclerotic events in the simvastatin plus ezetimibe group compared to placebo.
Conclusions: Reducing LDL cholesterol with a treatment regimen of simvastatin plus ezetimibe safely reduced the incidence of major atherosclerotic events in patients with moderate to severe CKD.

Renin Angiotensin System Blockade and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Proteinuria: A Meta-Analysis
Am Heart J 2008;155:791-805
Purpose: To evaluate the role of RAS blockade in improving cardiovascular CV outcomes in patients with CKD.
Study Selection: RCT that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (ACEI/ARB). RAS blockade-based therapy was compared with placebo and control therapy (β-blocker, calcium-channel blockers, and other antihypertensive-based therapy) in the study.
Results: Twenty-five trials (n=45758) were included. Compared to placebo, RAS blockade reduced the risk of heart failure in patients with diabetic nephropathy. In patients with non-diabetic CKD, RAS blockade decreased CV outcome compared to control therapy.
Conclusions: RAS blockade reduced CV outcomes in diabetic nephropathy as well as non-diabetic CKD.

Hypertension

- see Family Medicine, FM37
- HTN occurs in about 20% of population
- etiology classified as primary ("essential;" makes up 90% of cases) or secondary
- primary HTN can cause kidney disease (hypertensive ischemic nephropathy), which may in turn exacerbate the HTN
- secondary HTN can be caused by renal parenchymal or renal vascular disease

Hypertensive Nephrosclerosis

Table 16. Chronic vs. Malignant Hypertension

	Chronic Nephrosclerosis	Malignant Nephrosclerosis
Histology	Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles	Fibrinoid necrosis of arterioles, disruption of vascular endothelium
Clinical Picture	Black race (ApoL1 mediated hypertension nephrosclerosis), underlying CKD, chronic hypertensive disease	Acute elevation in BP (dBP >120 mmHg) HTN encephalopathy, acute end organ damage (papilledema, stroke, ACS, AKI)
Urinalysis	Mild to severe proteinuria, normal urine sediment	Proteinuria and hematuria (RBC casts)
Therapy	Blood pressure control, (target <120/80) with frequent follow-up	Lower dBP to 100-110 mmHg within 6-24 h More aggressive treatment can cause ischemic event Identify and treat underlying cause of HTN
Prognosis	Can progress to renal failure if HTN poorly controlled	Lower survival if renal insufficiency develops

Effects of Intensive BP Control in CKD
J Am Soc Nephrol 2017;28(9):2812-2823
Purpose: To evaluate appropriate target for BP in patients with CKD and HTN.
Methods: RCT subgroup analyses of participants in the Systolic Blood Pressure Intervention Trial (SPRINT). Participants were randomly assigned to intensive group (sBP <120 mmHg) or standard group (sBP <140 mmHg).
Results: The intensive group had a lower rate of all-cause death (HR 0.72, 95% CI 0.63-1.05) and major CV events (HR 0.81, 95% CI 0.63-1.05). Decreases in eGFR were comparable between treatment groups (HR 0.90, 95% CI 0.44-1.83). Treatment effects did not differ between participants with and without CKD.
Conclusions: In patients with CKD and HTN without diabetes, target sBP of 120 mmHg vs. 140 mmHg reduced rates of major CV events and all-cause death.

Renovascular Hypertension

- see *Vascular Diseases of the Kidney, NP31*

Renal Parenchymal Hypertension

- HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include:
  - excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective sodium excretion with fluid overload

Investigations

- as well as investigations for renovascular HTN, additional tests may include
  - 24 h urinary estimations of CrCl and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy (very rarely if at all)

Treatment

- most chronic renal disease is irreversible; however, treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na^+-restriction (2 g/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor K^+ and Cr) if there is significant proteinuria (>300 mg/d)

Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population >50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive), and acquired cystic kidney disease (in chronic hemodialysis patients)

Adult Polycystic Kidney Disease

- autosomal dominant; at least 2 genes: *PKD1* (chr 16p) and *PKD2* (chr 4q)
- PKD1 (1:400), PKD2 (1:1000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant *PKD* gene but accumulate a series of second 'somatic hits' precipitating the condition
- PKD gene defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth
- most common extrarenal manifestations: multiple asymptomatic hepatic cysts (33%), mitral valve prolapse (25%), intracranial arterial aneurysm (10%), diverticulosis, hernias (abdominal/inguinal)

Hypercalcemia complicates many cancers and can cause multiple kinds of renal disorders (renal vasoconstriction with reduced GFR, salt-wasting with volume depletion, risk of calcium kidney stones)

- polycystic liver disease rarely causes liver failure, but may form the indication of liver transplant due to space occupying impact which can lead to reduced oral intake and malnutrition
- less common extrarenal manifestations: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta

Signs and Symptoms
- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain (source: infection of renal cysts, hemorrhaging into cysts, kidney stones)
- hematuria (frequently initial sign is microscopic hematuria, otherwise gross hematuria)
- nocturia (urinary concentrating defect)
- extrarenal presentation (e.g. ruptured berry aneurysm, diverticulitis, mitral valve prolapse, aortic regurgitation, tricuspid valve prolapse)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- ± palpable kidneys

Common Complications
- urinary tract and cyst infections, HTN, chronic renal failure, nephrolithiasis (5-15%), flank and chronic back pain

Clinical Course
- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10x normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

Investigations
- U/S is confirmatory (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdomen with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- MRI for kidney volume measurement
- gene linkage analysis for *PKD1* for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)

Treatment
- non-pharmacological:
  - educate patient and family about disease, its manifestations, and inheritance pattern
  - genetic counseling: transmission rate 50% from affected parent
  - avoid contact sports due to greater risk of injury to enlarged kidneys
- pharmacological:
  - monitor blood pressure and treat HTN with ACEI (target ≤ 110/75 mmHg)
  - encourage free water intake >2-3L/d to reduce endogenous ADH levels (ADH promotes cyst growth)
  - tolvaptan (vasopressin receptor (V2R) antagonist) has been used to slow the decline of renal function (18-50 y/o, eGFR >45, TKV >750 mL), however, its use has been limited by side effects
  - TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
  - dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
  - may require nephrectomy for symptomatic relief of pain or due to recurrent infections
- complication prevention:
  - adequate hydration to prevent stone formation
  - screen for cerebral aneurysms if family history of aneurysmal hemorrhages
  - prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)

Extrarenal Manifestations of PKD
Hepatic cysts
Mitral valve prolapse
Cerebral aneurysms
Diverticulosis

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease
NEJM 2017;377:1930-1942
Purpose: To evaluate the efficacy and safety of the vasopressin V2-receptor antagonist tolvaptan in patients with later-stage autosomal dominant polycystic kidney disease.
Methods: Phase III, randomized withdrawal, multicentre, placebo-controlled, double-blind trial.
Results: Change in estimated GFR from baseline was -2.34 ml/min/1.732 in the tolvaptan group (95% CI, -2.81 to -1.87) vs. -3.61 ml/min/1.732 m^2in the placebo group (95% CI, -4.08 to -3.14).
Conclusions: Tolvaptan resulted in a slower decline than placebo in the estimated GFR over a 1 yr period.

Autosomal Recessive Polycystic Kidney Disease
- 1 in 20000 incidence
- prenatal diagnosis by enlarged kidneys (due to cystic dilatation of the collecting ducts); if significant in utero can result in Potter sequence
- perinatal death from respiratory failure
- associated with hepatic fibrosis
- patients who survive perinatal period develop CHF, HTN, CKD, portal hypertension
- treated with dialysis, kidney, and/or liver transplant

Medullary Sponge Kidney
- common, autosomal dominant, usually diagnosed in 4th-5th decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria, and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney

- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP leading to characteristic radial pattern ("bouquet of flowers"), "Swiss cheese" appearance on histological cross-section
- treat UTIs and stone formation as indicated
- does not result in renal failure

End Stage Renal Disease

Definition
- ESRD represents an irreversible decline in kidney function requiring renal replacement therapy
- glomerular filtration rate less than 15 mL/min/1.73 m^2 body surface area

Risk Factors
- amount of daily proteinuria (strongest predictor of progression to ESRD)
- hypertension, age, history of chronic renal insufficiency, DM, tobacco, analgesic use, ethnicity (increased incidence in Black individuals), lower socioeconomic status, obesity, hyperuricemia, and family history of kidney disease

Presentation of End Stage Kidney Disease

1. Volume Overload
- due to increase in total body Na^+ content
- signs: weight gain, HTN, pulmonary, or peripheral edema

2. Electrolyte Abnormalities
- high
  - K^+ (decreased renal excretion, medications including RAAS blockers, diet with high K)
  - PO_4^{3-} (decreased renal excretion)
- low
  - Ca^{2+} (decreased vitamin D activation, hyperphosphatemia, hypoalbuminemia)
  - HCO_3^- (inability of kidney to excrete the acid load and generate bicarb)

3. Uremic Syndrome
- manifestations result from retention of uremic toxins as well as hormone deficiencies

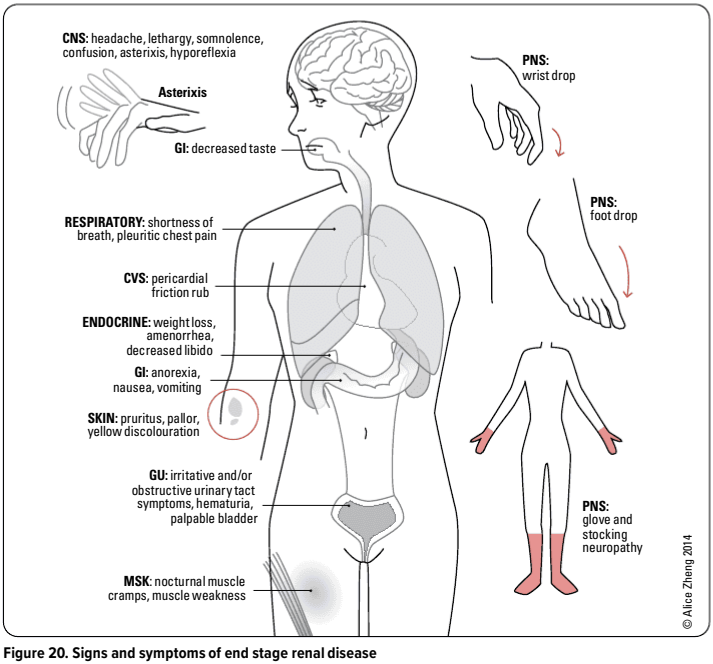
CNS: headache, lethargy, somnolence, confusion, asterixis, hyporeflexia
Asterixis
GI: decreased taste
RESPIRATORY: shortness of breath, pleuritic chest pain
CVS: pericardial friction rub
ENDOCRINE: weight loss, amenorrhea, decreased libido
GI: anorexia, nausea, vomiting
SKIN: pruritus, pallor, yellow discolouration
GU: irritative and/or obstructive urinary tact symptoms, hematuria, palpable bladder
MSK: nocturnal muscle cramps, muscle weakness
PNS: wrist drop
PNS: foot drop
PNS: glove and stocking neuropathy
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Figure 20. Signs and symptoms of end stage renal disease

Complications
- CNS: encephalopathy, decreased LOC, stupor, seizure
- cardiovascular system: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
- endocrine
  - decreased testosterone, estrogen, progesterone
  - increased FSH, LH
  - insulin resistance, decreased insulin requirements
  - hypertriglyceridemia, accelerated atherogenesis
- metabolic: anion gap and non anion gap metabolic acidosis
- renal osteodystrophy: secondary increased PTH due to decreased Ca^{2+}, high PO_4^{3-}, and low active vitamin D (1,25-OH vitamin D3)
  - osteitis fibrosa cystica
- dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular Ca^{2+}deposition)

Treatment
- therapies include, dialysis, renal transplant or non-dialytic conservative management
- dialysis is the preferred treatment for ESRD
- initiation of chronic dialysis has major implications on patients and healthcare system

Renal Replacement Therapy

Dialysis

Indications for Dialysis in Chronic Kidney Disease

Table 17. Indications for Dialysis

Absolute Indications	Relative Indications
Volume overload*	Anorexia and dysgeusia
Hyperkalemia*	Decreased cognitive functioning
Severe metabolic acidosis*	Profound fatigue and weakness
Neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures)	Severe anemia unresponsive to erythropoietin
Uremic pericarditis	Persistent severe pruritus
Refractory accelerated HTN	Restless leg syndrome
Clinically significant bleeding diathesis	
Persistent severe N/V	

*Unresponsive to medications

- there are 2 types of dialysis:
  - hemodialysis and hemodiafiltraion (both are blood based therapies)
  - peritoneal dialysis
- outpatient dialysis can be done in centre (hospital) or at home (PD and Home hemodialysis).
- decision to start dialysis in ESRD should be symptom driven or when GFR reaches approximately ≤10 mL/min
- hemodialysis:
  - blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  - available as intermittent (e.g. 3-6x/wk), which are in-hospital treatments
  - can be delivered at home or in-centre, nocturnal
  - vascular access can be achieved through a central venous catheter, an artificial AV graft, or an AV fistula
- patients with CKD should be referred for vascular access surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350 µmol/L, or within 1 yr of an anticipated need
- check Kidney Failure Risk Equation, which provides the 2 and 5 year probability of treated kidney failure for a potential patient with CKD stage 3 to 5
- peritoneal dialysis: peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  - available as continuous ambulatory (CAPD; 2-5 exchanges/d) or automated PD (using cycler machine at night)
- refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)

How to Write Dialysis Orders (MUST BE INDIVIDUALIZED)
- Filter Type (e.g. F80)
- Length (e.g. 4 h 3x/wk or 2 h daily)
- Q Blood Flow (max 500 cc/min)
- Ultrafiltration (e.g. 2 L or to target dry weight)
- Na+ 140 (can be adjusted by starting at 155 and "ramping" down to minimize cramping)
- K + (based on serum K+)

Serum K+	Dialysate
4-6	1.5
3.5-4	2.5
<3.5	3.5

- Ca^{2+} 1.25
- HCO_3^- 40
- Heparin (none, tight [500 U/h] or full [1000 U/h])
- IV fluid to support BP (e.g. NS)

When to Initiate Dialysis
CrCl <20 mL/min
- Educate patient regarding risks and benefits of dialysis; discuss goals of care, especially in frail older patients.
- if patient indicates preference for hemodialysis, make arrangements for AV access (fistula or graft)

CrCl <10 mL/min
- Dialysis should be initiated when patient has uremic symptoms or refractory metabolic/ electrolyte abnormalities

NOTE
A preemptive transplant can be considered if patient has a living don

Source:
National Kidney Foundation Kidney Disease Outcomes Quality Initiative.
Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, et al. A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis. NEJM. 2010 Aug 12;363(7):609–19.

Commonly Used Immunosuppressive Drugs

Calcineurin inhibitors
- Cyclosporine
- Tacrolimus

Antiproliferative medications
- Mycophenolate mofetil
- Azathioprine

Other agents
- Sirolimus
- Prednisone

Anti-lymphocyte antibodies
- Thymoglobulin
- Basiliximab

Indications for Dialysis (Refractory to Medical Therapy)

AE IOU
Acidosis
Electrolyte imbalance (K+)
Intoxication (AKI)
Overload (fluid)
Uremia (encephalopathy, pericarditis, urea >35-50 mM)

Table 18. Peritoneal Dialysis vs. Hemodialysis

	Peritoneal Dialysis	Hemodialysis
Rate	Slow	Fast
Location	Home	Home or in-centerdialysis unit
Ultrafiltration	Osmotic pressure via dextrose dialysate	Hydrostatic pressure
Solute Removal	Concentration gradient and convection	Concentration gradient and convection
Membrane	Peritoneum	Semi-permeable artificial membrane (e.g Polysulfone)
Method	Indwelling catheter in peritoneal cavity	Blood flowed extracorporeally through dialysis machine
Complications	Infection at catheter site Bacterial Peritonitis Metabolic effects of glucose Encapsulating peritoneal sclerosis (rare)	Central venous stenosis/ thrombosis Bacteremia (catheter related) Bleeding due to heparin Hemodynamic stress of extracorporeal circuit Disequilibrium syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/ water flux over short time) - usually during first few dialysis sessions at start of ESKD
Preferred When	Residual renal function Success depends on presence of residual renal function Hemodynamic instability	Intraperitoneal adhesions Home conditions non-conducive

Renal Transplantation

- provides maximum replacement of GFR
- only done for end stage renl disease and not AKI
- best way to reverse uremic signs and symptoms
  - renal transplantation has been shown to have improved long-term patient survival and greater quality of life over dialysis
- native kidneys usually left in situ
- 2 types: deceased donor, living donor (related or unrelated)
- living donor transplants are associated with better short- and long-term outcomes than deceased donor transplants
- kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- induction immunosuppression with IV thymoglobulin or basiliximab, followed by maintenance oral immunosuppression with an oral immunosuppression cocktail (usually corticosteroids, calcineurin inhibitor, anti-metabolite)
- long-term monitoring of cyclosporine and tacrolimus levels are required
- 1 yr renal allograft survival rates ≥90%

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis
NEJM 2019;380:447-458
Purpose: To assess the use of high doses of iron in patients undergoing hemodialysis.
Study: Multi-centre, open-label trial with blinded endpoint evaluation.
Population: 2141 adults with ESRD in whom maintenance hemodialysis was initiated no more than 12 mo prior were randomized to high-dose IV iron (median 264 mg monthly) administered proactively (1,093) or low-dose IV iron (median 145 mg monthly) administered reactively (1,048).
Outcome: Primary endpoint was nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death.
Results: 29.3% of patients in the high-dose group had a primary endpoint event, compared to 32.3% in the low-dose group. Patients in the high-dose group had a lower median monthly dose of an erythropoiesis-stimulating agent compared to the low-dose group (29,757 IU vs. 38,805 IU).
Conclusions: A high-dose IV iron regimen administered proactively in patients undergoing hemodialysis is superior to a low-dose regimen administered reactively.

Complications

- #1 cause of mortality in transplanted patients is cardiovascular disease
- increased risk of infections (bacterial, viral, fungal, opportunistic)
- new-onset DM (often due to prednisone and calcineurin inhibitors, especially tacrolimus)
- graft rejection (cellular or humoral)
- acute rejection: rise in Cr, fever, hematuria, graft site tenderness, oliguria, although symptoms are very uncommon
- early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
- transplant glomerulopathy from antibody injury
- cyclosporine or tacrolimus nephropathy (see *Small Vessel Disease, NP32*)
- *de novo* GN (membranous, IgA, MPGN)
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss
- leading causes of late allograft loss: interstitial fibrosis/tubular atrophy and death with functioning graft
- depends on immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset DM)
- infections (CMV, PJP, and other opportunistic infections usually occur between 1 and 6 mo post-transplant)
- malignancy (skin cancer, Kaposi's sarcoma, non-Hodgkin's lymphoma)

Common Medications

Table 19. Common Medications in Nephrology

Classification	Examples	Site of Action	Mechanism of Action (Secondary Effect)	Indication	Dosing	Adverse Effects
Loop Diuretics	furosemide (Lasix®) bumetanide (Bumex®/ Burinex®) ethacrynate (Edecrin®) torsemide (Demadex®)	Thick ascending limb of Loop of Henle	↓ Na^+/K^+ /2Cl-transport ± renal and peripheral vasodilatory effects (K^+loss; ↑ H^+secretion; ↑ Ca^{2+}excretion)	Management of edema secondary to CHF, nephrotic syndrome, cirrhotic ascites; ↑ free water clearance (e.g. in SIADH-induced hyponatremia), ↓ BP (less effective due to short action)	furosemide: edema: 20-80 mg IV/IM/PO q6-8h (max 600 mg/d) until desired response HTN: 20-80 mg/d PO once daily/ BID dosing IV furosemide is equivalent to 2 x po dose	Allergy in sulfa-sensitive individuals Electrolyte abnormalities; hypokalemia, hyponatremia, hypocalcemia, hypercalciuria (with stone formation) Volume depletion with metabolic alkalosis Precipitates gout attacks
Thiazide Diuretics	hydrochlorothiazide (HCTZ) chlorothiazide (Diuril®) indapamide (Lozol®, Lozide®) metolazone (Zaroxolyn®) chlorthalidone (Hygroton®)	Distal convoluted tubule	Inhibit Na^+/Cl-transporter (K^+ loss; ↑ H^+ secretion; ↓ Ca^{2+} excretion)	1st line for essential HTN Treatment of edema Idiopathic hypercalciuria and stones Diabetes insipidus (nephrogenic)	HCTZ: edema: 25-100 mg PO once daily HTN: 12.5-25 mg PO once daily (max 50 mg/d) nephrolithiasis/hypercalciuria: 25-100 mg once daily	Hypokalemia Increased serum urate levels Precipitates gout attacks, hypercalcemia Elevated lipids Glucose intolerance
Potassium-Sparing Diuretics	spironolactone (Aldactone®) triamterene (Dyrenium®) amiloride (Midamor®)	Cortical collecting duct (↓ Na^+ reabsorption)	Aldosterone antagonist (spironolactone) Block Na^+ channels (triamterene and amiloride)	Reduces K^+ loss caused by other diuretics Edema/hypervolemia Severe CHF, ascites (spironolactone), cystic fibrosis (amiloride ↓ viscosity of secretions)	spironolactone: 25-200 mg/d once daily/BID dosing HTN: 50-200 mg/d once daily/BID dosing Hyperaldosteronism: 100-400 mg/d once daily/BID dosing amiloride: edema/HTN: 5-10 mg PO once daily	Hyperkalemia (caution with ACEI) Triamterene can be nephrotoxic (rare) Nephrolithiasis Gynecomastia (estrogenic effect of spironolactone)
Osmotic Diuretics	mannitol (Osmitrol®) glycerol urea	Renal tubules (proximal and collecting duct)	Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate – inhibits reabsorption of water and ↑ urinary excretion of toxic material	To ↓ intracranial or intraocular pressure Mobilization of excess fluid in renal failure or edematous states	mannitol: ↓ ICP: 0.25-2 g/kg IV over 30-60 min	Transient volume expansion Electrolyte abnormalities (↓/↑ Na^+, ↓/↑ K^+)
ACEI	ramipril (Altace®) enalapril (Vasotec®) lisinopril (Prinivil®) trandolapril (Mavik®) captopril (Capoten®)	Lungs Tissues diffusely	Inhibits angiotensin converting enzyme, preventing formation of angiotensin II Prevents angiotensin II vasoconstricting vascular smooth muscle ➔ net vasodilation ➔ ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules ➔ ↑ Na^+ and H_2O excretion ➔ ↓ BP Reduces fibrosis and atherogenesis	HTN Cardioprotective effects Renoprotective effects	ramipril: HTN: 2.5-10 mg PO once daily/BID dosing renoprotective use; 10 mg PO once daily trandolapril: HTN; 1-4 mg PO once daily	Cough Asthma Hyperkalemia Angioedema Agranulocytosis (captopril) AKI Teratogenic
ARB	losartan (Cozaar®) candesartan (Atacand®) irbesartan (Avapro®) valsartan (Diovan®) telmisartan (Micardis®) eprosartan (Teveten®) olmesartan (Olmetec®)	Vascular smooth muscle, adrenal cortex, proximal tubules	Competitive inhibitor at the angiotensin II receptor: prevents angiotensin II vasoconstricting action on vascular smooth muscle ➔ ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules ➔ ↑ Na^+ and H_2O excretion	HTN Cardioprotective effects Renoprotective effects	HTN: losartan 25-100 mg PO once daily candesartan 8-32 mg PO once daily irbesartan 150-300 mg PO once daily valsartan 80-320 mg PO once daily telmisartan 20-80 mg PO once daily eprosartan 400-800 mg PO once daily olmesartan 20-40 mg PO once daily	Hyperkalemia Caution – reduce dose in hepatic impairment AKI Teratogenic

Landmark Nephrology Trials

Trial Name	Reference	Clinical Trial Details
ELECTROLYTE DISTURBANCES		
BICAR ICU	Lancet 2018; 392:31-40	**Title**: Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomized controlled, phase 3 trial **Purpose**: To assess the potential benefits of sodium bicarbonate infusion on outcomes in critically ill patients. **Methods**: A multicenter, open-label, randomized controlled phase 3 trial was conducted in 26 ICUs in France. Critically ill adult patients with severe acidaemia were randomly assigned to receive sodium bicarbonate infusion or no treatment. The primary outcome measured death and organ failure. **Results**: 389 patients were enrolled in the study. The primary outcome occurred in 71% of the control group and 66% of the bicarbonate group. The probability of survival at day 28 was not significantly different between the groups, except for patients in the Acute Kidney Injury Network stratum. Adverse events were more common in the bicarbonate group, but no life-threatening complications were reported. **Conclusions**: Sodium bicarbonate had no effect on the primary outcome in patients with severe metabolic acidaemia, but benefited those with acute kidney injury.
SALT-1	NEJM 2006;16:2099-112	**Title**: Tolvaptan, a Selective Oral Vasopressin V2-Receptor Antagonist, for Hyponatremia **Purpose**: Investigate whether tolvaptan might be of benefit in hyponatremia. **Methods**: Patients with euvolemic or hypervolemic hyponatremia were randomized to oral tolvaptan 15 mg daily or oral matched placebo. The primary endpoints were changes in daily area-under-the-curve for serum Na^+ concentrations. **Results**: Serum Na^+ concentrations increased more in the tolvaptan group than placebo during the first 4 d ($P<0.001$) and after 30 d ($P<0.001$). Side effects included dry mouth, thirst, and increased urination. **Conclusions**: In patients with euvolemic or hypervolemic hyponatremia, tolvaptan, an oral vasopressin V2-receptor antagonist, was effective in increasing serum Na^+ concentrations.
SMART	NEJM 2018; 378:829-39	**Title**: Balanced Crystalloids versus Saline in Noncritically Ill Adults **Purpose**: To examine the clinical impact of using balanced crystalloids compared to saline for routine intravenous fluid therapy in noncritically ill adults in the emergency department. **Methods**: In a single-center trial, noncritically ill adults in the emergency department received either balanced crystalloids or saline for intravenous fluid therapy. The study assessed hospital-free days and major adverse kidney events as outcomes. **Results: 13,347 patients were enrolled, receiving either balanced crystalloids or saline in the emergency department. Hospital-free days were similar between the groups. However, the incidence of major adverse kidney events within 30 d was lower in the balanced crystalloids group compared to saline.** **Conclusions**: No disparity in hospital-free days was observed between balanced crystalloids and saline treatments in noncritically ill adults receiving intravenous fluids.
OPAL-HK	NEJM 2015;372:211-21	**Title**: Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors **Purpose**: Assess the safety and efficacy of patiromer, a K^+ binder, in treating hyperkalemia. **Methods**: Patients with CKD receiving RAAS inhibitors with serum K^+ levels of 5.1 to 6.5 mmol/L received patiromer for 4 wk. The primary efficacy endpoint was the mean change in serum K^+ levels from baseline to week 4. Subsequently, 107 patients were randomly assigned to patiromer or placebo for the randomized withdrawal phase. **Results**: The median increase in K^+ levels from baseline was greater with placebo than with patiromer ($P<0.001$). A recurrence of hyperkalemia occurred in 60% of placebo patients compared with 15% in the patiromer group, **Conclusions**: In CKD patients receiving RAAS inhibitors and who had hyperkalemia, patiromer treatment was associated with a decrease in serum K^+ levels and a reduction in hyperkalemia recurrence.
DIABETIC NEPHROPATHY		
ACEI and Diabetic	NEJM 1993;329:1456-62	**Title**: The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy **Purpose**: Determine whether captopril has kidney-protecting properties independent of BP control in patients with diabetic nephropathy. **Methods**: Patients with insulin-dependent DM were randomized to captopril or placebo. The primary endpoint was a doubling of the baseline serum Cr. **Results**: The associated risk reductions of the primary endpoint was 48% in the captopril group. Serum Cr concentrations doubled in 25 patients in the captopril group compared to 43 patients in the placebo group. The mean rate of decline in Cr clearance was 11% per yr in the captopril group and 17% in the placebo group. **Conclusions**: Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than BP control alone.
BENEDICT	NEJM 2004;351:1941-51	**Title**: Preventing Microalbuminuria in Type 2 Diabetes **Purpose**: Assess whether ACEI and non-dihydropyridine calcium channel blockers (CCBs), alone or in combination, prevent microalbuminuria in patients with HTN and T2DM. **Methods**: 1204 patients were randomized to 3 yr of treatment with trandolapril 2 mg daily plus verapamil SR 180 mg daily, trandolapril alone, verapamil alone, or placebo. The primary endpoint was the development of persistent microalbuminuria. **Results**: The primary outcome was reached in 5.7% of combination patients, 6% of trandolapril patients, 11.9% of verapamil patients, and 10% of placebo patients. Serious adverse events were similar among all treatment groups. **Conclusions**: Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with T2DM and HTN with normoalbuminuria.
DETAIL	NEJM 2004;351:1952-61	**Title**: Angiotensin-Receptor Blockade versus Converting–Enzyme Inhibition in Type 2 Diabetes and Nephropathy **Purpose**: Compare renoprotective effects of ARBs and ACEIs in patients with T2DM. **Methods**: 250 patients with T2DM and early nephropathy were randomized to either telmisartan 80 mg daily or enalapril 20 mg daily. The primary endpoint was a change in GFR between baseline and last available value, during the 5 yr study period. **Results**: At 5 yr, the change in GFR was -17.9 mL/min/1.73 m^2 with telmisartan, compared with 14.9 mL/min/1.73 m^2 with enalapril (difference -3.0 mL/min/1.73 m^2; 95% CI -7.6 to 1.6). **Conclusions**: The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in T2DM with mild to moderate HTN and early nephropathy.
IDNT	NEJM 2001;345:851-60	**Title**: Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes **Purpose**: Assess whether the ARB irbesartan or the CCB amlodipine slow progression of nephropathy in patients with T2DM independently of BP effects. **Methods**: 1715 hypertensive patients with nephropathy due to T2DM were randomized to irbesartan 300 mg daily, amlodipine 10 mg daily, or placebo. The primary endpoint was a composite of the doubling of baseline serum Cr, development of ESRD, or all-cause mortality. **Results**: Treatment with irbesartan was associated with a rate of primary endpoints 20% lower than placebo ($P=0.02$) and 23% lower than amlodipine ($P=0.006$). Treatment with irbesartan was associated with a RR of ESRD 23% lower than that in both other groups ($P=0.07$ for both comparisons). These differences were not explained by BP changes. **Conclusions**: Treatment with irbesartan reduced the risk of developing ESRD and worsening renal function in patients with T2DM and diabetic nephropathy.

Trial Name	Reference	Clinical Trial Details
RENAAL	NEJM 2001;345:861-69	**Title**: Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy **Purpose**: Assess the role of ARB losartan in slowing progression of renal disease, in patients with T2DM and nephropathy. **Methods**: 1513 patients were randomized to losartan 50-100 mg daily or placebo, in addition to conventional antihypertensive treatments. The primary outcome was a composite of the doubling of serum Cr, ESRD, or mortality. **Results**: 327 patients in the losartan group, compared with 359 in the placebo group, achieved the primary endpoint (risk reduction 16%; P=0.02). Losartan reduced the incidence of the doubling of serum Cr (risk reduction 25%; P=0.006) and ESRD (risk reduction 28%; P=0.002), with no effect on mortality. **Conclusions**: Losartan conferred significant renal benefits in patients with T2DM and nephropathy, and was generally well-tolerated.
ROADMAP	NEJM 2011;364:907-17	**Title**: Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes **Purpose**: Assess whether treatment with an ARB would prevent the occurrence of microalbuminuria in T2DM patients with normoalbuminuria. **Methods**: 4447 patients with T2DM were randomized to receive olmesartan 40 mg OD or placebo. Additional hypertensives were used as needed to meet the target BP of <130/80 mmHg. The primary outcome was the time until the first onset of microalbuminuria. **Results**: Microalbuminuria developed in 8.2% of olmesartan-treated patients, and 9.8% in the placebo group. The time to onset of this increase was increased by 23% with olmesartan (hazard ratio 0.77; 95% CI 0.63 to 0.94; P=0.01). **Conclusions**: The use of the ARB olmesartan was more effective than placebo in delaying the onset of microalbuminuria in patients with T2DM, normoalbuminuria, and good BP control.
VA-NEPHRON D	NEJM 2013; 369: 1892-903	**Title:** Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy **Purpose:** To compare the safety and effectiveness of combining an ACE inhibitor and an ARB versus ARB monotherapy in proteinuric diabetic nephropathy progression. **Methods:** Patients with T2DM, urinary albumin-to-creatinine ratio ≥300, and estimated GFR of 30.0-89.9 ml/min/1.73 m^2 received losartan. They were then randomly assigned to lisinopril or placebo. The primary outcome was a decline in estimated GFR, ESRD, or death. The secondary outcome was a decline in estimated GFR or ESRD. Safety outcomes were also assessed. **Results:** The study was halted early due to safety concerns. Among 1448 patients with a median follow-up of 2.2 years, there was no significant difference in the primary endpoint between monotherapy and combination therapy groups. The trend towards a secondary endpoint benefit decreased over time. Combination therapy increased the risk of hyperkalemia and acute kidney injury. **Conclusions:** The combination of an ACE inhibitor and an ARB in patients with diabetic nephropathy was linked to higher adverse event risks.
PARENCHYMAL KIDNEY DISEASES		
AASK	JAMA 2001;285:2719-28	**Title**: Effect of Ramipril vs. Amlodipine on Renal Outcomes in Hypertensive Nephrosclerosis **Purpose**: Compare the effects of an ACEI, a dihydropyridine CCB and β-blocker on hypertensive renal disease progression. **Methods**: 1094 patients with hypertensive renal disease were randomized to amlodipine 5-10 mg/d, metoprolol 50-200 mg/d or ramipril 2.5-10 mg/d, with other agents. The primary outcome was the rate of change of GFR. **Results**: The ramipril group had a 36% slower mean decline in GFR (P=0.006) vs. the amlodipine group (95% CI 20% to 66%). There were no significant differences in the mean GFR decline from baseline to 3 yr between treatment groups. **Conclusions**: Ramipril, compared with amlodipine, slows progression of hypertensive renal disease and proteinuria, and may benefit patients without proteinuria as well.
AURORA 1	Lancet 2021; 397(10289): 2070-80	**Title**: Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial **Purpose**: Evaluate the safety and efficacy of voclosporin in the treatment of lupus nephritis. **Methods**: Adults diagnosed with systemic lupus erythematosus with lupus nephritis (biopsy class III-V) were randomized (1:1 ratio) to receive oral voclosporin or placebo, in addition to standard therapy. The primary outcome at wk 52 was a complete renal response (urine protein: Cr ratio ≤0.5 mg/mg, stable renal function (eGFR ≥60 mL/min/1.73 m2 or <20% decrease from baseline eGFR), and no rescue therapy). **Results**: At endpoint wk 52, significantly more patients in the voclosporin group had a complete renal response, as compared to the placebo group (41% vs. 23%; OR 2.65; 95% CI 11.64-4.27; P<0.0001). The adverse event profile was similar between groups (21% vs. 21%) with no deaths attributable to study-related treatments. **Conclusions**: Patients who received voclosporin in addition to standard therapy had a higher rate of complete renal response than those receiving standard therapy alone.
BLISS-LN	NEJM 2020;383:1117-28	**Title**: Two Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis **Purpose**: Elucidate the efficacy and safety of IV belimumab as compared with placebo, when added to standard therapy of mycophenolate mofetil or cyclophosphamide-azathioprine. **Methods**: Adults with biopsy-proven, active lupus nephritis were randomized (1:1 ratio) to receive IV belimumab (10 mg/kg) or matching placebo, in addition to standard therapy. The primary outcome at week 104 was a primary efficacy renal response (urinary protein: Cr ratio ≤0.7, eGFR no <20% pre-flare value, or ≥60 mL/min and no use of rescue therapy). **Results**: At endpoint wk104, significantly more patients in the belimumab group had a primary efficacy response, as compared to the placebo group (43% vs. 32%; OR 1.65; 95% CI 1.1 to 2.5; P=0.02). The risk of a renal-related event or death was lower among patients who received belimumab than placebo (hazard ratio 0.51; 95% CI 0.34 to 0.77; P=0.001). **Conclusions**: Patients who received belimumab in addition to standard therapy had a higher rate of primary efficacy response than those who received standard therapy alone.
CORAL	NEJM 2014;370:13-22	**Title**: Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis **Purpose**: Study the usefulness of renal artery stenting for the prevention of major adverse renal and CV events in patients with atherosclerotic renal artery stenosis. **Methods**: 947 patients with atherosclerotic renal artery stenosis and either systolic HTN or CKD were randomized to medical therapy plus stenting, or to medical therapy alone. The primary outcomes were occurrence of adverse CV and renal events. **Results**: The rate of primary events did not differ significantly between participants who underwent stenting or medical therapy alone (35.1% vs. 35.8%; hazard ratio 0.94; 95% CI 0.76 to 1.17; P=0.58). There were no significant differences in other components of the primary endpoint. **Conclusions**: Renal-artery stenting did not confer a significant benefit with respect to the prevention of renal or cardiac events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease.
MAINRITSAN	NEJM 2014;371:1771-80	**Title**: Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis **Purpose**: Assess whether rituximab helps maintain remission of ANCA-associated vasculitis. **Methods**: Patients with newly diagnosed ANCA-associated vasculitides in complete remission were randomized to either rituximab 500 mg or daily azathioprine. The primary endpoint at 28 mo was the rate of major relapse. **Results**: At 28 mo, major relapse occurred in 29% of patients in the azathioprine group, compared to 5% of patients in the rituximab group (hazard ratio 6.61; 95% CI 1.56 to 27.96; P=0.002). The frequency of serious adverse events was comparable between groups. **Conclusions**: More patients with ANCA-associated vasculitis had sustained remission at 28 mo with rituximab than with azathioprine.

Trial Name	Reference	Clinical Trial Details
ONTARGET	Lancet 2008;372:547-53	**Title**: Renal Outcomes with Telmisartan, Ramipril, or Both, in People at High Vascular Risk **Purpose**: Investigate the renal effects of ACEI, ARB and combination, in patients with atherosclerotic vascular disease for the reduction of proteinuria. **Methods**: 25 620 patients were randomized to ramipril 10 mg daily, telmisartan 80 mg daily, or a combination. The primary renal outcome was a composite of dialysis, doubling of serum Cr, and mortality. **Results**: The number of primary events were similar for telmisartan (13.4%) and ramipril (13.5%), (hazard ratio 1.00; 95% CI 0.92 to 1.09) but were increased with combination therapy (14.5%; hazard ratio 1.09; 95% CI 1.01 to 1.18, P=0.037). **Conclusions**: Telmisartan and ramipril monotherapy reduced proteinuria and Cr increase in patients with high vascular risk.
PEXIVAS	NEJM 2020;382:622-31	**Title: Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis** **Purpose**: To assess the effectiveness of plasma exchange versus no plasma exchange in terms of mortality or ESRD in patients with severe ANCA-associated vasculitis. **Methods**: A randomized trial with 2-by-2 factorial design assessing plasma exchange and two oral glucocorticoid regimens in severe ANCA-associated vasculitis. The primary outcome was a composite of death or ESRD. The follow-up period was up to 7 years. **Results**: Death or ESRD rates were 28.4% in the plasma-exchange group and 31.0% in the control group, showing no significant difference. The reduced-dose glucocorticoid regimen was non-inferior to the standard-dose regimen for death or ESRD. The reduced-dose group had fewer serious infections, but other outcomes were similar between the groups. **Conclusions**: Plasma exchange did not reduce death or ESRD in severe ANCA-associated vasculitis. The reduced-dose glucocorticoid regimen was as effective as the standard dose.
REIN	Lancet 1999;354:359-64	**Title**: Renoprotective Properties of ACE-inhibition in Non-diabetic Nephropathies with Non-Nephrotic Proteinuria **Purpose**: Assess the renoprotective effects of ACE inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. **Methods**: 186 patients were randomized to ramipril or control (placebo plus conventional antihypertensive). The primary endpoints were change in GFR and time to overt proteinuria. **Results**: The decline in monthly GFR was not significantly different (0.26 mL/min/1.73 m ²in ramipril group vs. 0.29 mL/min/1.73 m ²in the control group). Progression to ESRD was significantly less common with ramipril than control, for a RR of 2.72 (95% CI 1.22 to 6.08), likewise for progression to overt proteinuria (RR 2.40; 95% CI 1.27 to 4.52). **Conclusions**: In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria.
REIN2	Lancet 2005;365:939-46	**Title**: Blood-Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease **Purpose**: Assess effects of intensified vs. conventional BP control with ACEI on progression to ESRD. **Methods**: Patients with non-diabetic nephropathies receiving background treatment were randomized to either conventional (diastolic <90 mmHg) or intensified (<130 mmHg) BP control. The primary outcome was time to ESRD over 36 mo. **Results**: Patients assigned to intensified BP control progressed to ESRD at a rate of 23% compared to 20% in the control group. **Conclusions**: In patients with non-diabetic nephropathy already on ACEI, there was no further benefit from intensified BP control by adding CCB vs. conventional BP control on ACEI alone.
ROAD	JASN 2007;18:1889-98	**Title**: Renoprotection of Optimal Antiproteinuric Doses **Purpose**: Determine whether titration of benazepril or losartan would improve renal outcomes in chronic renal insufficiency. **Methods**: 360 patients without DM, who had proteinuria and chronic renal insufficiency were randomized to benazepril 10 mg/d, benazepril 20 mg/d, losartan 50 mg/d, or losartan 100 mg/d. The primary endpoint was time to a composite of doubling serum Cr, ESRD, or mortality. **Results**: Up-titration of benazepril and losartan were associated with a 51% and 53% reduction in the primary endpoint risk (P=0.028 and 0.022 respectively). There was no significant difference in the rates of major adverse events between treatment groups. **Conclusions**: Up-titration of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without DM who had proteinuria and renal insufficiency.
AMACING	Lancet 2017;389:1312-22	**Title**: Prophylactic Hydration to Protect Renal Function from Intravascular Iodinated Contrast Material in Patients at High Risk of Contrast-Induced Nephropathy **Purpose**: Assess clinical effectiveness of prophylactic hydration in preventing contrast-induced nephropathy in patients with compromised renal function. **Methods**: High-risk adult patients undergoing an elective procedure requiring iodinated contrast were randomized to IV NaCl 0.9% or no prophylaxis. The primary outcome was incidence of contrast-induced nephropathy. **Results**: Contrast-induced nephropathy was recorded in 2.6% of non-hydrated patients and 2.7% of hydrated patients. **Conclusions**: No-hydration prophylaxis was non-inferior and cost-saving in preventing contrast-induced nephropathy compared with IV hydration.
CHRONIC KIDNEY DISEASE		
CHOIR	NEJM 2006;355:2085-98	**Title**: Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease **Purpose**: Determine the optimal level of Hb correction in CKD with erythropoietin (EPO) deficiency as a complication. **Methods**: 1432 patients with CKD were randomized to receive epoetin alfa (human recombinant EPO) targeted to Hb 13.5 g/dL, or those receiving epoetin alfa targeted to Hb 11.3 g/dL. The primary endpoint was a composite of death, MI, hospitalization for CHF, and stroke. **Results**: 125 primary events occurred in the high-Hb group compared to 97 events in the low-Hb group (hazard ratio 1.34; 95% CI 1.03 to 1.74; P=0.03). More patients in the high-Hb group had at least one serious adverse event. **Conclusions**: A higher Hb correction target resulted in increased rates of infarction, hospitalization for CHF, and stroke.
CLICK	NEJM 2021; 385:2507-19	**Title**: Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease **Purpose**: Understand the safety and efficacy of thiazide diuretic chlorthalidone for the treatment of HTN in patients with advanced CKD. **Methods**: 160 patients with stage 4 CKD and poorly controlled HTN were randomized (1:1 ratio) to receive chlorthalidone or placebo. The primary outcome measure was the change in 24-h ambulatory sBP from baseline to 12 wk post-treatment. **Results**: Patients with advanced CKD and poorly controlled CKD receiving chlorthalidone experienced a greater reduction in sBP than those receiving placebo therapy (-11.0 mmHg vs. -0.5 mmHg; P<0.001). Adverse events, including hypokalemia, hyperglycemia, dizziness, and hyperuricemia occurred more frequently in patients receiving chlorthalidone. **Conclusions** : In patients with advanced CKD and poorly controlled HTN, chlorthalidone more effectively reduces sBP than placebo, however, adverse events must be carefully considered.
CREATE	NEJM 2006;355:2071-84	**Title**: Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia **Purpose**: Establish whether correction of anemia in stage 3 or 4 CKD improves CV outcomes. **Methods**: 603 patients with eGFR 15.0 to 35.0 mL/min/1.73 m2 and mild-moderate anemia were randomized to a normal target Hb (13-15 g/dL) or a subnormal target range (10.5-11.5 g/dL). The primary endpoint was a composite of 8 CV events. **Results**: Complete correction of anemia did not affect the likelihood of a first CV event (hazard ratio 0.78; 95% CI 0.53 to 1.14; P=0.20). The mean eGFR was 24.9 mL/min/1.73 m²in the complete group, and 24.2 mL/min/1.73 m2 in the incomplete group, decreasing by 3.6 and 3.1 mL/min/1.73 m²/yr, respectively. **Conclusions**: In patients with CKD, complete correction of Hb did not reduce the risk of CV events or incidence of hypertensive episodes.

Trial Name	Reference	Clinical Trial Details
CREDENCE	NEJM 2019;380:2295-306	**Title**: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) **Purpose**: Since few effective treatments are available for diabetic nephropathy, this study aims to assess renal outcomes in patients treated with SGLT2 inhibitor canagliflozin. **Methods**: Patients with type 2 diabetes and albuminuric CKD were randomized to receive canagliflozin 100 mg daily, or placebo. All patients had an estimated GFR of 30 to <90 mL/min/1.73 $m^2$and albuminuria >300 to 5000, and were treated with RAAS blockade. The primary outcome was a composite of ESRD (dialysis, transplantation, or sustained eGFR <15mL/min/1.73 m^2), a doubling of serum Cr, or death from renal or CV (CV) causes. **Results**: Of 4401 randomized patients with a median follow-up of 2.62 yr, the RR of primary outcome was 30% lower in the canagliflozin group than in the placebo group (hazard ratio 0.70; 95% CI 0.59 to 0.82; P=0.00001). The canagliflozin group also had a lower risk of CV death, MI or stroke (hazard ratio 0.85; 95% CI 0.67 to 0.95; P=0.01). **Conclusions**: In patients with T2DM and kidney disease, the risk of kidney failure and CV events was lower in the canagliflozin group than in the placebo group.
DAPA-CKD	NEJM 2020; 383:1436-46	**Title**: Dapagliflozin in Patients with Chronic Kidney Disease **Purpose**: Elucidate the safety of dapagliflozin in patients with CKD with or without T2DM. Methods: 4304 patients with CKD (eGFR 25-73 mL/min/1.73 $m^2$and ACR 200-5000) were randomized to receive dapagliflozin or placebo. The **Methods** outcome was a composite of ≥50% reduction in eGFR, ESRD, and death from cardiorenal causes. Results: The primary outcome occurred less frequently in patients receiving dapagliflozin compared to those receiving placebo (9,2% vs. 14.5%; HR 0.61; 95% CI 0.51-0.72; P<0.001; NNT to prevent one primary outcome event 19; 95% CI 15-27). This trial was stopped early because of efficacy. **Conclusions**: Patients receiving dapagliflozin are less likely to experience a composite of ≥50% reduction in eGFR, ESRD, or death from cardiorenal causes compared to those receiving placebo. Dapagliflozin is safe in patients with CKD.
EMPA-CKD	NEJM 2023;388:117–27	**Title**: Empagliflozin in Patients with Chronic Kidney Disease **Purpose**: To evaluate the impact of empagliflozin on patients with CKD who are at risk of disease progression, encompassing a wide range of individuals. **Methods**: 6609 participants were randomly assigned to receive empagliflozin (10mg once daily) or placebo. Participants had CKD with different levels of kidney function. The primary outcome assessed kidney disease progression or cardiovascular-related death. **Results**: During a median 2.0 years of follow-up, the empagliflozin group (13.1%) had a lower occurrence of primary outcome events compared to the placebo group (16.9%). There were fewer hospitalizations in the empagliflozin group, but no significant effect on heart failure or cardiovascular death. Rates of serious adverse events were similar. **Conclusions**: Empagliflozin decreased the risk of kidney disease progression or cardiovascular death in a broad range of patients at risk of CKD progression.
FIDELIO-DKD	NEJM 2020;383:2219-29.	**Title**: Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes **Purpose**: Understand the effects of finerenone on kidney and cardiovascular outcomes in patients with CKD and T2DM. Methods: 5734 patients with CKD (diabetic retinopathy + urine ACR 30-300 + eGFR 25-60 mL/min/1.73 m^2or urine ACR 300-5000 + eGFR 25-75 mL/min/1.73 m2) and T2DM were randomized (1:1 ratio) to receive finerenone or placebo. The primary outcome measure was a composite of kidney failure, ≥40% reduction in eGFR, and death from renal causes. Results: The primary outcome occurred less frequently in patients receiving finerenone compared to those receiving placebo (17.8% vs. 21.1%; HR 0.82; 95% CI 0.73-0.93; P=0.001). The frequency of adverse events was comparable between groups, though hyperkalemia-related discontinuation of therapy occurred more frequently in patients receiving finerenone. **Conclusions**: Patients receiving finerenone are less likely to experience a composite of kidney failure, ≥40% reduction in eGFR, and death from renal causes compared to those receiving placebo.
SHARP	Lancet 2011;377:2181-92	**Title**: The Effects of Lowering LDL Cholesterol with Simvastatin plus Ezetimibe in Patients with Chronic Kidney Disease **Purpose**: Assess safety and efficacy of low-density lipoprotein (LDL)-lowering with simvastatin plus ezetimibe in patients with CKD. **Methods**: 9270 patients with moderate-severe CKD with no history of MI or coronary revascularization were randomized to simvastatin 20 mg plus ezetimibe 10 mg daily, or to matching placebo. The primary outcome was the first major atherosclerotic event. **Results**: Combination therapy resulted in a 17% reduction in first major atherosclerotic events (11.3% vs. 13.4%; RR 0.83; 95% CI 0.74 to 0.94; P=0.0021). There were significant reductions in non-hemorrhagic strokes (2.8% vs. 3.8%; RR 0.75; 95% CI 0.60 to 0.94; P=0.01) and arterial revascularization (6.1% vs. 7.6%; RR 0.79; 95% CI 0.68 to 0.93; P=0.0036). **Conclusions**: In patients with CKD and no history of MI or coronary revascularization, 20 mg simvastatin plus 10 mg ezetimibe daily, compared to matching placebo, reduced the incidence of major atherosclerotic events.
SPRINT	NEJM 2015; 373:2103-16	**Title**: A Randomized Trial of Intensive versus Standard Blood-Pressure Control **Purpose**: To compare the effectiveness of treating systolic blood pressure to a target below 120 mmHg versus treating it to a target below 140 mmHg. **Methods**: A randomized trial including 9361 individuals with elevated cardiovascular risk without diabetes were assigned to either an intensive (target <120 mmHg) or standard (target <140 mmHg) systolic blood pressure treatment. The primary outcome included various cardiovascular events. **Results**: After 1 year, the intensive-treatment group achieved a lower mean systolic blood pressure of 121.4 mmHg compared to 136.2 mmHg in the standard-treatment group. The trial was stopped early due to significantly lower rates of the primary composite outcome and all-cause mortality in the intensive-treatment group. However, the intensive-treatment group experienced higher rates of certain serious adverse events. **Conclusions**: Targeting a systolic blood pressure below 120 mm Hg in high-risk, non-diabetic patients reduced cardiovascular events but increased some adverse events.
TEMPO 3:4	NEJM 2012;367:2407-18	**Title**: Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease **Purpose**: To determine the annual rate of change in the total kidney volume. **Methods**: 1445 Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients aged 18-50 randomly assigned 2:1 to receive tolvaptan or placebo in Phase 3 double-blind, multicenter, and placebo-controlled trial lasting 3 years. The primary endpoint was annual rate of change in total kidney volume. Secondary endpoints included a composite of clinical progression and rate of kidney-function decline. **Results**: Over a 3-year period, tolvaptan resulted in a slower increase in total kidney volume (2.8% per year) compared to placebo (5.5% per year). Tolvaptan showed better outcomes in the composite endpoint, with lower rates of worsening kidney function, kidney pain, and a slower decline in kidney function. Tolvaptan had fewer ADPKD-related adverse events but more discontinuations due to aquaresis and hepatic issues. **Conclusions**: Tolvaptan slowed kidney volume increase and function decline but had higher discontinuation rates due to adverse events in ADPKD.
TREAT	NEJM 2009;361:2019-32	**Title**: A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease **Purpose**: Assess clinical outcomes with darbepoetin alfa among patients with T2DM and CKD. **Methods**: 4038 patients with diabetes, CKD and anemia were randomized to darbepoetin alfa at 13 g/dL, or to placebo. The primary endpoints were the composite outcomes of death, CV event, death, or ESRD. **Results**: Death or CV events occurred in 632 patients treated with darbepoetin alfa and 602 placebo-matched patients (hazard ratio 1.05; 95% CI 0.94 to 1.17; P=0.41). Death or ESRD occurred in 652 patients treated with darbepoetin alfa and 618 placebo-matched patients (hazard ratio 1.06; 95% CI 0.95 to 1.19; P=0.29). **Conclusions**: Darbepoetin alfa did not reduce the risk of death, a CV event, or a renal event, and was associated with an increased risk of stroke.

Trial Name	Reference	Clinical Trial Details
EVOLVE	NEJM 2012; 367:2482-94	**Title**: Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis **Purpose**: Assess the effects of calcimimetic agent cinacalcet in reducing mortality risk and nonfatal CV events in patients with CKD. **Methods**: 3383 patients with moderate-severe hyperparathyroidism undergoing hemodialysis were randomized to cinacalcet or placebo. The primary composite endpoint was time until death, MI, hospitalization for unstable angina (UA), HF, or a peripheral vascular event. **Results**: The primary endpoint was reached in 48.3% of cinacalcet-treated patients and 49.2% of placebo-matched patients (hazard ratio 0.93; 95% CI 0.85 to 1.02; P=0.11). **Conclusions**: Cinacalcet did not significantly reduce the risk of death or major CV events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis.
CYSTIC DISEASES OF THE KIDNEY		
REPRISE	NEJM 2017;377:1930-42	**Title**: Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease **Purpose**: Assess the efficacy and safety of tolvaptan in patients with later-stage autosomal dominant polycystic kidney disease (ADPCKD). **Methods**: 1370 patients with ADPCKD with eGFR 25 to 44 mL/min/1.73 m^2were randomized (1:1 ratio) to tolvaptan or placebo for 12 mo. The primary endpoint was a change in eGFR from baseline to follow-up. **Results**: The change from baseline eGFR was -2.34 mL/min/1.73 m^2in the tolvaptan group (95% CI -2.81 to -1.87) compared with -3.61 mL/min/1.73 m2 in the placebo group (95% CI -4.08 to -3.14); (difference 1.27; 95% CI 0.86 to 1.86; P<0.001). **Conclusions**: Tolvaptan treatment in patients with later-stage ADPKD resulted in a slower decline in eGFR over a 1 yr period, compared to the placebo group.
RENAL REPLACEMENT THERAPY		
ALERT	Lancet 2003;361:2024-31	**Title**: Effect of Fluvastatin on Cardiac Outcomes in Renal Transplant Recipients **Purpose**: Evaluate the safety and efficacy of fluvastatin on cardiac and renal endpoints in renal transplant recipients. **Methods**: 2102 renal transplant patients were randomized to fluvastatin or placebo. The primary endpoint was the occurrence of a major CV event, including cardiac death, nonfatal MI, or coronary intervention. **Results**: Risk reduction in primary events was not significant with fluvastatin (risk ratio 0.83; 95% CI 0.64 to 1.06; P=0.139). There were fewer cardiac deaths and nonfatal MI in the fluvastatin group than in the placebo group (risk ratio 0.60; 95% CI 0.48 to 0.88; P=0.005). **Conclusions**: The use of fluvastatin in renal transplant recipients did not significantly decrease the risk of occurrence of a major adverse cardiac event, however, there was a significant reduction in cardiac deaths or nonfatal MI.
AURORA	NEJM 2009;360:1395-407	**Title**: Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis **Purpose**: Assess the benefit of statin therapy in patients undergoing hemodialysis for reduction of CV risk. **Methods**: 2776 patients undergoing maintenance hemodialysis were randomized to rosuvastatin 10 mg daily or placebo. The primary endpoint was death from CV causes, nonfatal MI, or stroke. **Results**: 9.2% and 9.5% of patients reached the primary endpoint, in the rosuvastatin and placebo groups, respectively (hazard ratio 0.96; 95% CI 0.84 to 1.11; P=0.59). Rosuvastatin had no effect on individual components of the primary endpoint. **Conclusions**: In patients receiving maintenance hemodialysis, rosuvastatin had no significant effect on CV risk.
ELITE-SYMPHONY	NEJM 2007;357:2562-75	**Title**: Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation **Purpose**: Evaluate the efficacy and relative toxic effects of four immunosuppressive agents in renal transplant recipients. **Methods**: 1645 renal-transplant recipients were randomized to receive standard-dose cyclosporine plus mycophenolate mofetil plus corticosteroids, or daclizumab induction plus mycophenolate mofetil plus corticosteroids, both groups in combination with either low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus. The primary endpoint was eGFR 12 mo after transplantation. **Results**: The mean eGFR was higher in patients receiving low-dose tacrolimus (65.4 mL/min/1.73 m^2) than in the 3 other groups (ranging from 56.7 mL/min/1.73 $m^2$to 59.5 mL/min/1.73 m^2). Serious adverse events were more common in low dose sirolimus than the other groups (53.2% vs. a range of 43.4% to 44.3%). **Conclusions**: Daclizumab induction, mycophenolate mofetil, corticosteroids, and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard calcineurin inhibitor (CNI) regimens.
FHN	NEJM 2010;363:2287-300	**Title**: Hemodialysis Six Times per Week versus Three Times per Week **Purpose**: Determine whether increasing the frequency of in-center hemodialysis would be beneficial. **Methods**: Patients were randomized to undergo hemodialysis 6x/wk or 3x/wk. The primary composite outcomes were death or change in left ventricular (LV) mass, and death or change in physical health scores. **Results**: Frequent hemodialysis was associated with significant benefits with respect to both primary outcomes (hazard ratio for LV mass 0.61; 95% CI 0.46 to 0.83; hazard ratio for physical health 0.70; 95% CI 0.53 to 0.92). Frequent hemodialysis was also associated with improved HTN and hyperphosphatemia control. **Conclusions**: Frequent hemodialysis, versus conventional hemodialysis, is associated with favourable patient outcomes.
HEMO	NEJM 2002;347:2010-19	**Title**: Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis **Purpose**: Assess the effects on morbidity and mortality of dialysis dose and level of flux, in patients undergoing maintenance hemodialysis. **Methods**: 1846 patients undergoing thrice-weekly dialysis were randomized to high-dose dialysis and to a low- or high-flux dialyzer. The primary outcome was all-cause mortality. **Results**: The primary outcome was not influenced by the dose or flux assignment; (RR 0.96; 95% CI 0.84 to 1.10; P=0.53) for a comparison of the high-dose group with standard-dose, and (RR 0.96; 95% CI 0.81 to 1.05; P=0.23) for a comparison of high- and low-flux dialyzer assignments. **Conclusions**: Use of high dose dialysis or high flux membranes vs. standard dose or low flux in 3x/wk dialysis does not improve survival or outcomes.
IDEAL	NEJM 2010;363:609-19	**Title**: A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis **Purpose**: Examine effects of timing dialysis initiation on survival in patients with CKD. **Methods**: Patients with CKD and eGFR 10 to 15 mL/min/1.73 m2 were randomized to early initiation (eGFR 10.0 to 14.0 mL/min/1.73 m^2) or late initiation (eGFR 5.0 to 7.0 mL/min/1.73 m2). The primary outcome was all-cause mortality. **Results**: A total of 37.6% of patients in the early initiation group and 36.6% of patients in the late-initiation group died within 3.59 yr (hazard ratio 1.04; 95% CI 0.83 to 1.30; P=0.75). There were no significant differences in the frequency of adverse events. **Conclusions**: In patients with progressive CKD, early initiation of dialysis was not associated with an improvement in survival or clinical outcomes.
CONVERT	Transplantation 2009;87:233-42	**Title**: Conversion from Calcineurin Inhibitors to Sirolimus Maintenance Therapy in Renal Allograft Recipients **Purpose**: Evaluate the efficacy and safety of converting maintenance renal transplant patients from CNIs to sirolimus. **Methods**: 830 renal allograft recipients were randomized to continue CNI or convert from CNI to sirolimus. Primary endpoints were GFR and the rates of biopsy-confirmed acute rejection (BCAR), graft loss, or death at 12 mo. **Results**: Intention-to-treat analysis showed no significant difference in GFR, while on-therapy analysis showed higher GFR at 12 and 24 mo after sirolimus conversion. Rates of other primary endpoints were similar between groups. Malignancy rates were significantly lower at 12 and 24 mo in patients who underwent sirolimus conversion. **Conclusions**: At 2 years, conversion of maintenance therapy in renal transplant patients from CNIs to sirolimus was associated with excellent patient and graft survival.

Trial Name	Reference	Clinical Trial Details
STARRT-AKI	NEJM 2020;383:240–51	**Title**: Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury **Purpose**: To evaluate and compare the impact of two strategies (accelerated initiation versus standard initiation) on critically ill patients with AKI. **Methods**: A multinational trial randomized critically ill patients with severe AKI to receive either accelerated or standard initiation of renal-replacement therapy, with the primary outcome as 90-day all-cause mortality. **Results**: Of 3019 patients, 97% were included in the analysis. The accelerated-strategy group had higher rates of renal-replacement therapy and adverse events. However, there was no significant difference in 90-day mortality between the accelerated and standard strategy groups. Survivors in the accelerated-strategy group had a higher dependence on renal-replacement therapy. **Conclusions**: The use of an accelerated renal-replacement strategy did not result in a lower 90-day mortality risk in critically ill patients with AKI.

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Neurology

Shadia Adekunte, Jacob Peller, Kayla Saul, and **Kristiana Xhima,** chapter editors
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Acronyms

AD	Alzheimer's disease
ADL	activities of daily living
ALS	amyotrophic lateral sclerosis
ASM	antiseizure medications
CIDP	chronic inflammatory demyelinating polyneuropathy
CJD	Creutzfeldt-Jakob disease
CN	cranial nerve
CNS	central nervous system
CSF	cerebrospinal fluid
CVD	cerebrovascular disease
DBS	deep brain stimulation
DLB	dementia with Lewy bodies
EEG	electroencephalography
EMG	electromyography
FDG-PET	fluorodeoxyglucose 18-F positron emission tomography
FTD	frontotemporal dementia
GBS	Guillain-Barré syndrome
GCA	giant cell arteritis
GCS	Glasgow coma scale
HD	Huntington's disease
IADL	instrumental activities of daily living
ICH	intracerebral hemorrhage
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
IVIG	intravenous immunoglobulin
LEMS	Lambert-Eaton myasthenic syndrome
LMN	lower motor neuron
LOC	level of consciousness
LP	lumbar puncture
MG	myasthenia gravis
MMSE	mini-mental state examination
MoCA	Montreal cognitive assessment
MS	multiple sclerosis
MSA	multiple system atrophy
NCD	neurocognitive disorder
NCS	nerve conduction study
NPH	normal pressure hydrocephalus
PD	Parkinson's disease
PNS	peripheral nervous system
RAPD	relative afferent pupillary defect
REM	rapid eye movement
SAH	subarachnoid hemorrhage
SSRI	selective serotonin reuptake inhibitor
TBI	traumatic brain injury
TCA	tricyclic antidepressant
TIA	transient ischemic attack
tPA	tissue plasminogen activator
UMN	upper motor neuron

Lesion Localization

- **CNS vs. PNS lesion**
  - CNS: cortical, subcortical, brainstem (midbrain, pons, medulla), cerebellum, spinal cord
  - PNS: nerve root, plexus, peripheral nerve, neuromuscular junction, muscle
  - see *Table 3, N4* for differentiating LMN, UMN and extrapyramidal lesions
- **cortical**
  - contralateral hemiparesis (with differential effect on face and arm vs. leg)
  - contralateral hemisensory loss, cortical sensory loss (graphesthesia, stereognosis)
  - dominant hemisphere: aphasia, alexia, agraphia, acalculia, left-right disorientation
  - non-dominant hemisphere: hemineglect, dysprosody, amusia, constructional apraxia, alien hand syndrome
  - homonymous hemianospia/quadrantanospia
  - gaze deviation (involvement of frontal eye field)
  - seizure
  - agnosia (visual, auditory)
  - ideomotor and ideational apraxia
- **subcortical**
  - internal capsule: contralateral hemiparesis with equal face, arm, and leg involvement without sensory/cortical deficits (pure motor); contralateral hemiparesis and sensory deficit (sensorimotor); contralateral dysmetria/clumsiness and paresis (ataxic hemiparesis); dysarthria and ataxia of the hand (clumsy hand-dysarthria syndrome)
  - basal ganglia: resting tremor, bradykinesia, festinating gait, hemiballism, chorea, dystonic posture
  - thalamus: dense sensory loss, contralateral severe pain, visual field defect, cognitive impairment, altered LOC
- **brainstem (midbrain, pons, medulla)**
  - crossed hemiplegia or hemisensory loss (i.e. ipsilateral face, contralateral body)
  - ipsilateral limb ataxia (dysmetria, impaired rapid alternating movements)
  - nystagmus, diplopia, ptosis, pupil abnormalities (miosis, mydriasis), gaze impairment, internuclear ophthalmoplegia
  - dysphagia, dysarthria
  - hearing loss, vertigo
  - ipsilateral Horner's syndrome
- **cerebellum**
  - symptoms ipsilateral to side of lesion
  - limb ataxia (dysmetria, intention tremor, dysdiadochokinesia, hypotonia causing pendular reflexes)
  - truncal ataxia (wide-based gait, inability to perform heel-to-toe gait, truncal titubation)
  - nystagmus, hypermetric or hypometric saccades, impaired smooth pursuit
  - scanning speech (explosive speech with noticeable pauses and accentuated syllables)
- **spinal cord**
  - LMN signs at level of lesion; UMN signs below level of lesion
  - sensory level (line below which there is sensory loss); suspended "cape-like" sensory level (in central cord lesions)
  - neurogenic bladder and bowel, sexual dysfunction
  - saddle anesthesia (involvement of conus medullaris)
  - sensory ataxia (involvement of dorsal columns)
- **nerve root**
  - multiple peripheral nerve involvement
  - myotomal/dermatomal deficits
  - back/neck pain radiating to limb
  - saddle anesthesia (involvement of cauda equina)

- **peripheral nerve**
  - length-dependent ("stocking-glove distribution") or non-length-dependent sensory loss (see *Peripheral Neuropathies, N38*)
  - weakness or sensory loss respecting the distribution of a specific nerve (e.g. median nerve, ulnar nerve, radial nerve)
- **neuromuscular junction**
  - fluctuating/fatigable symptoms
  - facial and limb weakness, bulbar (dysarthria, dysphonia, dysphagia), ocular (diplopia, ptosis), respiratory distress (see *Neuromuscular Diseases, N40*)
  - reflexes usually preserved unless severe/advanced or LEMS
- **muscle**
  - usually symmetric proximal weakness (e.g. climbing stairs, getting up from chair) without sensory deficits
  - asymmetric myopathic weakness seen in distal myopathies, myositis, glycogen storage diseases, and facioscapulohumeral dystrophy
  - myalgia, muscle atrophy

Neurological Exam

Mental Status Exam

- orientation (person, place, time)
- appearance, mood and affect
- language, attention (serial sevens, months backwards)
- LOC with GCS
  - score from 3-15 (eye opening/4, verbal response/5, motor response/6)
- memory
  - MMSE – /30 (normal: ≥24, mild impairment: 19-23, moderate impairment: 10-18, severe impairment: <10)
  - MoCA – /30 (normal: ≥26)

Table 1. Glasgow Coma Scale

Points	Eyes	Verbal	Motor
1	No eye opening	No verbal response	No motor response
2	Eye opening to pain	Incomprehensible sounds	Extension to pain
3	Eye opening to verbal stimulus	Inappropriate words	Flexion to pain
4	Eye opening spontaneously	Confused	Withdraws from pain
5		Oriented	Localizes pain
6			Obeys commands

Screening Neurologic Exam
Mental status: orientation (person, place, time), obeys commands, gcs
Cranial nerves: visual acuity, visual fields, pupils, eye movements, face sensation, muscles of facial expression, speech, swallowing, sternocleidomastoid, trapezius, tongue
Motor: tone, power, reflexes (biceps, triceps, patellar, ankle), special tests (plantar response, pronator drift)
Sensory: pain, temperature, vibration, proprioception
Coordination: finger-to-nose, heel-to-shin, rapid alternating movements
Gait: normal, heel-to-toe, pull test

Cranial Nerve Exam

Table 2. Cranial Nerve Exam and Associated Deficits

Cranial Nerve	Physical Exam	Deficit
Olfactory (CN I)	Test identification of common odorants (i.e. coffee) in each nostril	Anosmia (complete loss of smell), hyposmia (partial loss of smell)
Optic (CN II)	Visual acuity, visual fields, colour vision, Pupils: symmetry, direct and consensual pupillary-light reflex, swinging flashlight test for RAPD Fundoscopy	Vision loss, absence of pupillary-light reflex, RAPD, optic disc edema/pallor
Oculomotor (CN III)	Test eye movements Pupils: symmetry, direct and consensual pupillary-light reflex Observe eyelids	Oblique binocular diplopia, eye position "down and out," mydriasis, ptosis
Trochlear (CN IV)	Test eye movements (superior oblique performs intorsion, depression and abduction of eye)	Vertical binocular diplopia, hypertropia, contralateral head tilt
Trigeminal (CN V)	Test face sensation: V1 (forehead, corneal reflex), V2 (cheek), V3 (chin) Test muscles of mastication: palpate temporalis and masseter when jaw clenched, observe for jaw deviation on mouth opening, test jaw jerk reflex	Decreased facial sensation, absent corneal reflex, atrophy and weakness of muscles of mastication, jaw deviation to weak side
Abducens (CN VI)	Test eye movements (lateral rectus performs abduction of eye)	Horizontal binocular diplopia, abduction deficit, esotropia
Facial (CN VII)	Test muscles of facial expression (raise eyebrows, close eyes tightly, smile with teeth showing) Test corneal reflex (efferent limb) Test taste in anterior 2/3 of tongue	Unilateral facial weakness (ipsilateral to LMN lesion, contralateral with forehead sparing in UMN lesion), decreased lacrimation, decreased salivation, hyperacusis, loss of taste from anterior 2/3 of tongue

If patient has not brought their glasses, have them look through a pinhole for best corrected vision

Innervation of Extraocular Muscles
CN III: superior rectus, inferior rectus, medial rectus, inferior oblique
CN IV: superior oblique
CN VI: lateral rectus

Contraction of the left sternocleidomastoid turns the head right

Table 2. Cranial Nerve Exam and Associated Deficits

Cranial Nerve	Physical Exam	Deficit
Vestibulocochlear (CN VIII)	Hearing: whisper, Rhinne and Weber tests Vestibular function: observe for nystagmus during eye movements, caloric test	Hearing loss, vertigo, nystagmus
Glossopharyngeal (CN IX)	Test swallowing, test gag reflex (afferent limb), test taste in posterior 1/3 of tongue	Mild oropharyngeal dysphagia, absent gag reflex, loss of taste from posterior 1/3 of tongue
Vagus (CN X)	Ask patient to open mouth, observe for soft palate and uvula, test swallowing, listen to speech for vocal cord function, test gag reflex (efferent limb)	Oropharyngeal dysphagia, hoarseness, dysarthria, soft palate drooping, contralateral uvula deviation, vocal cord paralysis, absent gag reflex
Accessory (CN XI)	Test strength of sternocleidomastoid (head turn) Test strength of trapezius (shoulder shrug)	Ipsilateral shoulder shrug weakness Contralateral head turn weakness
Hypoglossal (CN XII)	Ask patient to stick out tongue Inspect for deviation, atrophy and fasciculations Test strength through cheek	Tongue deviation to weak side on protrusion, atrophy, fasciculations

Caloric Test
Uses vestibulo-ocular reflex to test vestibular function
Cold fluid causes nystagmus towards contralateral ear
Warm fluid causes nystagmus towards ipsilateral ear

COWS: cold opposite, warm same

Motor Exam

- inspection
  - muscle bulk: atrophy, hypertrophy, asymmetry
  - abnormal movements: tremor, chorea, dystonia, dyskinesia, hemiballism, myoclonus, athetosis, tics, fasciculations, myokymia
  - abnormal posturing: flexor/decorticate (upper limb flexion and lower limb extension), extensor/decerebrate (limb extension)
- muscle tone
  - passively move a joint (i.e. elbow, wrist) and feel for resistance
  - hypotonia, hypertonia (spasticity, rigidity, paratonia)
- muscle power
- reflexes
  - upper limb reflexes (biceps, triceps, brachioradialis)
  - lower limb reflexes (patellar, ankle)
  - pathological reflexes (clonus, plantar response, Hoffmann's reflex)
- special tests (pronator drift, Holmes rebound phenomenon)

UMN Tests
Plantar response: normal is a flexor plantar response, abnormal is an extensor plantar response (Babinski sign) involving big toe extension
Pronator drift: with upper limbs extended in front, unable to keep them supinated with eyes closed
Hoffmann's reflex: flicking nail of middle finger causes reflexive flexion of thumb

Table 3. Differentiating LMN, UMN and Extrapyramidal Lesions

	LMN	UMN	Extrapyramidal
Muscle Tone	Hypotonia	Spasticity (hypertonia that is velocity-dependent)	Rigidity (hypertonia that is not velocity-dependent)
Muscle Atrophy	Significant denervation atrophy	Disuse atrophy over time	Variable
Reflexes	Decreased (hyporeflexia or areflexia)	Increased (hyperreflexia)	Variable
Plantar Reflex	Flexor plantar response	Extensor plantar response (Babinski sign)	Flexor plantar response
Involuntary Movements	Fasciculations	None	Tremor, chorea, hemiballism, myoclonus

Muscle Power Grading	
5	Normal power
4	Movement against gravity with some resistance (range 4-, 4, 4+)
3	Movement against gravity only
2	Movement with gravity eliminated
1	Flicker of contraction
0	No muscle contraction

Table 4. Overview of Neuromuscular Diseases

	Motor Neuron Disease (e.g. ALS)	Peripheral Neuropathy	Neuromuscular Junction Disorder	Myopathy
Signs and Symptoms				
Weakness	Segmental and asymmetrical, distal to proximal	Distal (except GBS) usually symmetrical	Proximal and fatigable (e.g. MG), or weak then recovers (e.g. LEMS)	Proximal (with some exceptions)
Fasciculations	Yes	Yes	No	No
Reflexes	Mixture of hyperreflexia and hyporeflexia or areflexia	Hyporeflexia or areflexia	Normal	Normal (until late)
Sensory	No	Yes	No	No
Autonomic	No	Yes	No (except LEMS)	No
Tests				
EMG	Denervation and reinnervation	Signs of demyelination and/or axonal loss	Decremental response on repetitive nerve stimulation, jitter on single fibre EMG	Small, short motor potentials
NCS	Normal or abnormal	Abnormal	Normal	Normal
Creatine Kinase	Normal or mildly increased	Normal	Normal	Increased (early/mid-stage) Normal/decreased (late stage)

Reflex	Muscle	Spinal Nerve	Peripheral Nerve
Biceps reflex	Biceps brachii	C5, C6	Musculocutaneous nerve
Triceps reflex	Triceps brachii	C7	Radial nerve
Brachioradialis reflex	Brachioradialis	C5, C6	Radial nerve
Patellar (knee) reflex	Quadriceps femoris	L2, L3, L4	Femoral nerve
Ankle (Achilles) reflex	Gastrocnemius and soleus	S1, S2	Tibial nerve
L2/3			Hip adductors
L3/4			Knee extensors
S1/2			Ankle (Achilles)

Reflex Grading	
0	Absent (areflexia)
1+	Decreased (hyporeflexia)
2+	Normal
3+	Increased (hyperreflexia)
4+	Increased with clonus (≥4 beats)

Table 5. Differentiating Radiculopathies and Peripheral Neuropathies

For each spinal nerve, learn two or more peripheral nerves and their associated actions/muscles.
In radiculopathies, all associated peripheral nerves (and their actions) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its actions) will be impaired.

Spinal Nerve	Peripheral Nerve	Action	Muscle
C5	Axillary	Shoulder abduction	Deltoid
C6	Musculocutaneous	Elbow flexion	Biceps brachii
	Radial	Wrist extension	Extensor carpi radialis longus
C7	Radial	Elbow extension	Triceps brachii
	Posterior interosseous	Finger extension	Extensor digitorum
	Median	Forearm pronation	Pronator teres
		Wrist flexion	Flexor carpi radialis
C8, T1	Median	Thumb flexion	Flexor pollicis longus
		Thumb abduction	Abductor pollicis brevis
		Opposition	Opponens pollicis
	Ulnar	Finger abduction	Dorsal interossei
	Radial	Index finger extension	Extensor indicis proprius
L2, L3, L4	Femoral	Hip flexion	Iliopsoas
		Knee extension	Quadriceps femoris
	Obturator	Hip adduction	Hip adductors
	Superior gluteal	Hip abduction	Tensor fasciae latae
L5	Tibial	Knee flexion	Hamstrings
		Ankle inversion	Tibialis posterior
	Superficial peroneal	Ankle eversion	Peroneus longus and brevis
	Deep peroneal	Ankle dorsiflexion	Tibialis anterior
		Big toe extension	Extensor hallucis longus
	Inferior gluteal nerve	Hip extension	Gluteus maximus
S1, S2	Tibial nerve	Ankle plantarflexion	Gastrocnemius and soleus

Cerebellar Signs and Symptoms
Limb ataxia: dysmetria, intention tremor, dysdiadochokinesia, hypotonia causing pendular reflexes, Holmes rebound phenomenon (if involvement of lateral zone of cerebellar hemisphere)
Truncal ataxia: wide-based gait and inability to perform heel-to-toe gait (if involvement of cerebellar vermis)
Eyes: nystagmus, hypermetric or hypometric saccades, impaired smooth pursuit
Speech: scanning speech

Romberg Test
Stable with eyes closed: normal
Unstable with eyes closed: positive Rhomberg, may indicate loss of proprioception
Sensory Exam

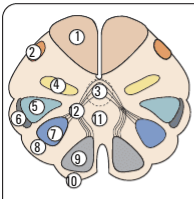
Sensory Exam

- **primary sensory modalities**
  - spinothalamic tract: pain and temperature
  - dorsal column-medial lemniscus pathway: fine touch, vibration, proprioception
- **cortical sensation**
  - graphesthesia, stereognosis, tactile extinction, 2-point discrimination
  - deficits in cortical sensation are often localized to the contralateral parietal lobe
- **Romberg test**
  - patient stands with eyes closed and feet together
  - instability may indicate loss of proprioception causing sensory ataxia

Coordination and Gait Exam

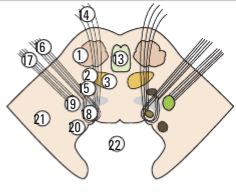
- **upper limb coordination**
  - finger-to-nose test
  - rapid alternating movements (repeatedly flip hand on palm of opposite hand)
- **lower limb coordination**
  - heel-to-shin test
  - rapid alternating movements (repeatedly tap foot on ground)
- **gait**
  - gait pattern: antalgic, hemiplegic, ataxic, apraxic, Parkinsonian, steppage, broad-based
  - heel-to-toe (tandem) gait
  - pull test for postural instability

Neuroanatomy Review



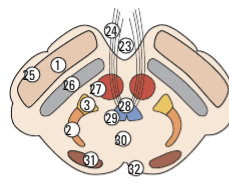
Medulla

1 Corticospinal tract
2 Spinothalamic tract
3 Medial lemniscus
4 Reticular formation
5 Spinal trigeminal nucleus
6 Spinal tract of trigeminal (V) nerve
7 Nucleus cuneatus
8 Fasciculus cuneatus
9 Nucleus gracilis
10 Fasciculus gracilis
11 Central canal



Pons

13 Pontine nuclei
14 Abducens nerve (CN VI)
15 Facial motor nucleus
16 Facial nerve (CN VII)
17 Trigeminal nerve (CN V)
18 Abducens nucleus (CN VI)
19 Nucleus of spinal tract of trigeminal (V) nerve
20 Lateral vestibular nucleus
21 Middle cerebellar peduncle
22 Fourth ventricle



Midbrain

23 Interpeduncular fossa
24 Oculomotor nerve (CN III)
25 Cerebral peduncle
26 Substantia nigra
27 Red nucleus
28 Edinger-Westphal nuclei
29 Oculomotor nucleus
30 Cerebral aqueduct
31 Pretectal area
32 Superior colliculus

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Figure 1. Brainstem (axial view)

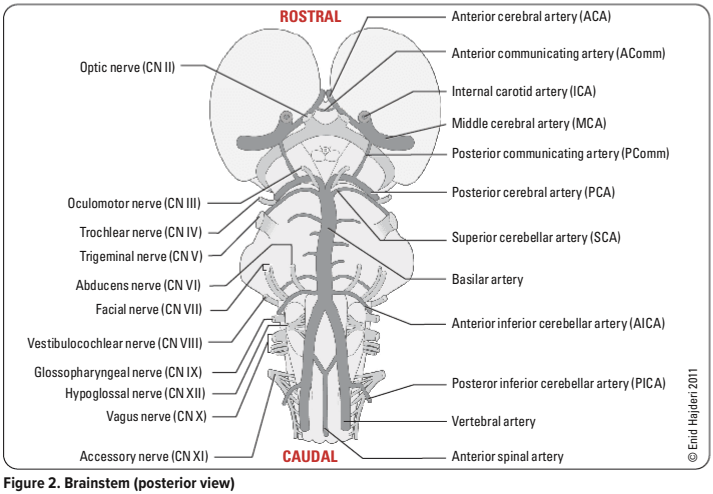

Figure 2. Brainstem (posterior view)

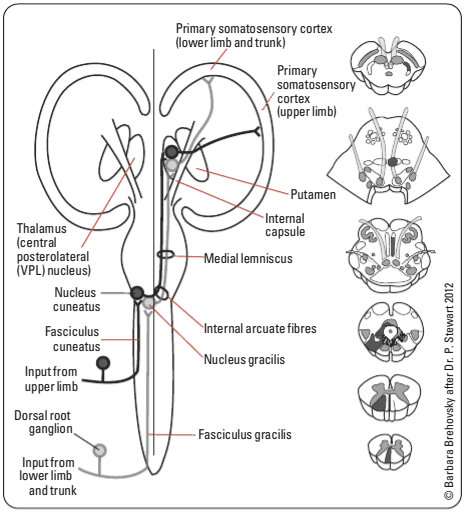

Figure 3. Discriminative touch pathway (dorsal column) from body

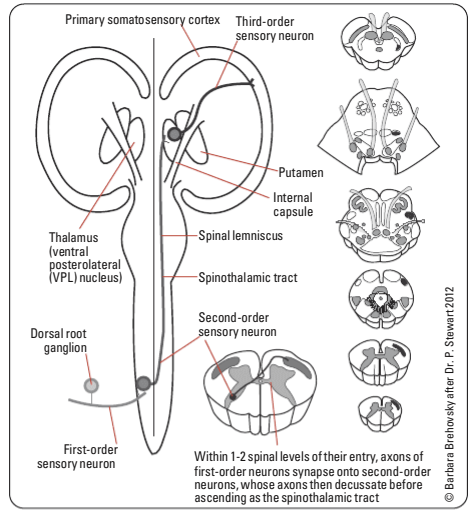
Primary somatosensory cortex
Third-order sensory neuron
Putamen
Internal capsule
Thalamus (ventral posterolateral (VPL) nucleus)
Spinal lemniscus
Spinothalamic tract
Second-order sensory neuron
Dorsal root ganglion
First-order sensory neuron
Within 1-2 spinal levels of their entry, axons of first-order neurons synapse onto second-order neurons, whose axons then decussate before ascending as the spinothalamic tract
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Figure 4. Spinothalamic tract from body

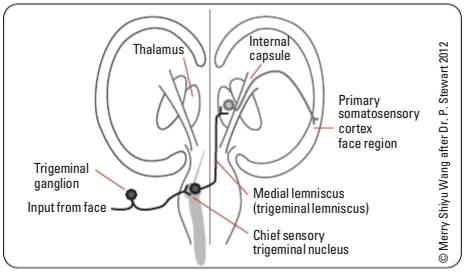


Figure 5. Discriminative touch pathway (dorsal column) from face

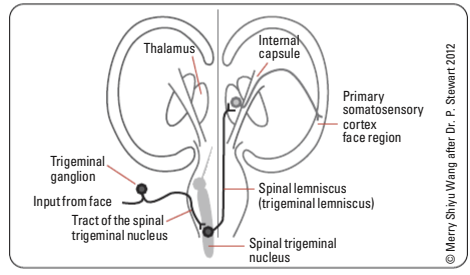


Figure 6. Spinothalamic tract pathway from face

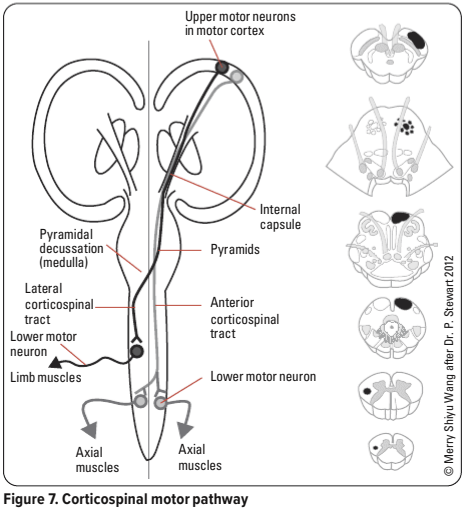


Figure 7. Corticospinal motor pathway

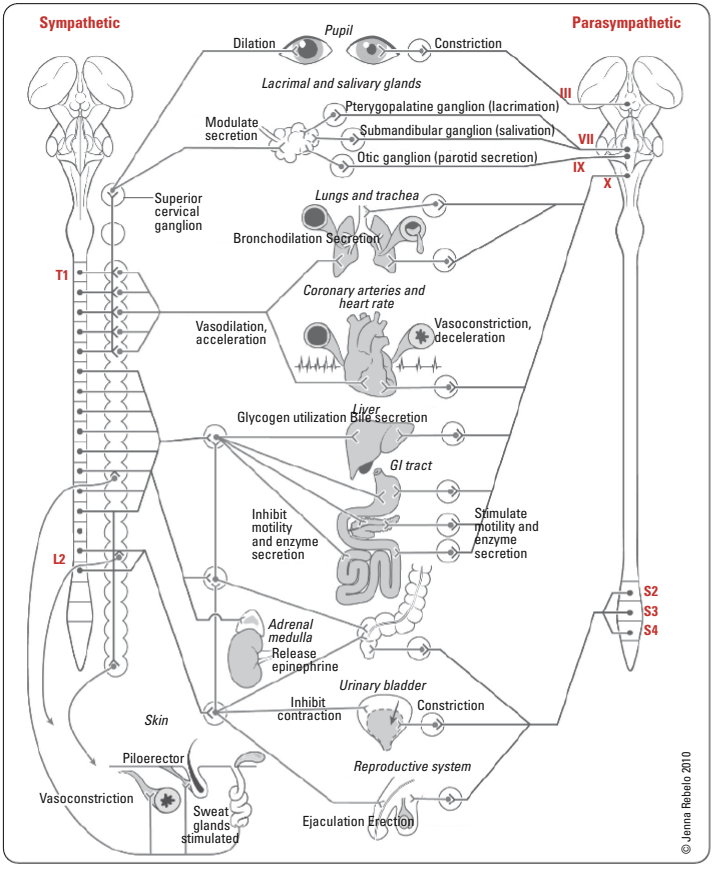


Figure 8. Sympathetic and parasympathetic pathways

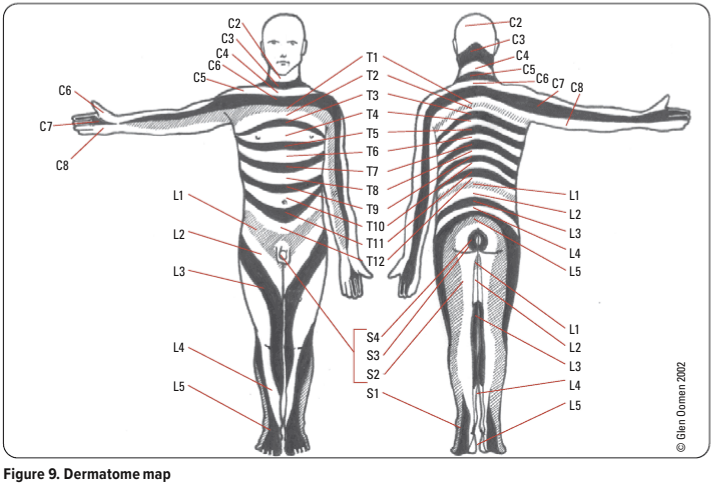


Figure 9. Dermatome map

Myotomes

- C5 – Shoulder abduction and elbow flexion
- C6 – Elbow flexion and wrist extension
- C7 – Elbow extension and finger extension
- C8 – Finger flexion
- T1 – Finger abduction
- T2-9 – Intercostal (abdominal reflexes)
- T9-10 – Upper abdominals
- T11-12 – Lower abdominals
- L2 – Hip flexion
- L3 – Hip adduction
- L4 – Knee extension and ankle dorsiflexion
- L5 – Ankle dorsiflexion and big toe extension
- S1 – Plantarflexion

Lumbar Puncture

Definition
- insertion of needle into lumbar cistern for removal of CSF or intrathecal administration of a substance

Indications
- diagnostic: CNS infection (meningitis, encephalitis), SAH (if CT head negative), IIH, NPH, CNS inflammatory disorder (MS, GBS, CNS vasculitis)
- therapeutic: decrease ICP, intrathecal administration of drugs (spinal anesthesia, chemotherapy, antibiotics)
- imaging: intrathecal administration of contrast for myelography or cisternography

Contraindications
- increased ICP in setting of mass, cerebral edema, or obstructive hydrocephalus (risk for cerebral herniation, CT head to rule out)
- skin infection at location for spinal needle insertion or suspected epidural abscess
- bleeding risk: severe thrombocytopenia (<50 x 109/L), high INR (>1.4), coagulopathy

The spinal needle for an LP is inserted into the L3-L4 or L4-L5 intervertebral space, which is below the conus medullaris of the spinal cord (L1-L2)

Complications
- post-LP headache (5-40%)
  - onset within 24-48 h, worse when upright, better when supineprevention: smaller gauge spinal needle (i.e. 22 G) , reinsert stylet prior to needle removal, blunt-ended needle
  - symptomatic treatment: oral analgesics, antiemetics, IV caffeine, sodium benzoate
  - definitive treatment: epidural blood patch
- localized back pain
- infection, bleeding (subdural hematoma, epidural hematoma)
- 6th nerve palsy (unilateral or bilateral, transient)
- epidermoid tumour (prevented by using spinal needle with stylet)
- tonsillar herniation (especiallly in setting of increased ICP)

Do not delay antibiotics while waiting for an LP if bacterial meningitis is suspected

CSF Opening Pressure
- measured using a manometer prior to collection of CSF
- patient positioning during measurement: lateral decubitus position, head neutral, legs extended
- normal CSF opening pressure
  - adults: 6-25 cmH_2O
  - children: 12-28 cmH_2O

RBC count in tube #1>>#4 → traumatic tap
RBC count in tube #1=#4 and elevated, or xanthohromic → SAH

CSF Analysis
- xanthochromia: yellow discolouration of CSF caused by bilirubin from the breakdown of RBCs, diagnostic of SAH
- tube #1: cell count (RBC count, WBC count and differential)
- tube #2: chemistry (protein and glucose)
- tube #3: microbiology (culture and sensitivity, Gram stain), additional tests depending on suspicion
  - viral: PCR for enterovirus, herpes simplex virus, varicella zoster virus, West Nile virus
  - bacterial: polysaccharide antigens of *H. influenzae, N. meningitidis, S. pneumoniae*, TB tests
  - fungal: cryptococcus antigen, fungal culture
- tube #4: cell count for comparison to tube #1

Table 6. CSF Interpretation

	Colour	Protein	Glucose	WBC Count	Other
Normal	Clear	0.15-0.60 g/L	60% of serum glucose (2.2-4.4 mmol/L)	Adults and children: <5 x 10^6/L neonates: <30 x 10^6/L	
Bacterial Meningitis	Cloudy	High (>1.0 g/L)	Normal or low	High (>1000 x 106/L, predominantly neutrophils)	High CSF opening pressure
Viral Meningitis	Clear	Normal or high (0.50-3.0 g/L)	Normal	High (<1000 x 10^6/L, predominantly lymphocytes)	Usually normal CSF opening pressure
Granulomatous Infection (tuberculosis, fungal)	Clear	High (usually <5.0 g/L)	Low	High (<1000 x 10^6/L, predominantly lymphocytes)	High CSF opening pressure in cryptococcal meningitis
Subarachnoid Hemorrhage	Xanthochromia or grossly bloody	High	Normal	High (from blood)	RBC count in tube #1=#4
Traumatic Tap	Grossly bloody	Normal	Slightly high	High (from blood)	RBC count in tube #1>>#4
Idiopathic Intracranial Hypertension	Clear	Normal	Normal	Normal	High CSF opening pressure
Normal Pressure Hydrocephalus	Clear	Normal	Normal	Normal	Normal CSF opening pressure
Multiple Sclerosis	Clear	Normal or slightly high	Normal	Normal or slightly high (predominantly lymphocytes)	Oligoclonal bands on CSF protein electrophoresis
Guillain-Barré Syndrome	Clear	High	Normal	Normal	Albuminocytologic dissociation (high protein, normal WBC count)
Leptomeningeal Disease	Clear	Normal or high	Normal or low	Normal or high lymphocytes	Presence of malignant cells on cytology

Approach to Common Presentations

Weakness

Approach

- **mode of onset**: abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (genetic, degenerative, endocrine, neoplastic)
- **course**: worse at onset (vascular), progressive (neoplastic, degenerative, infective, genetic), episodic (vascular, inflammatory), activity dependent (neuromuscular junction, muscular)
- **pattern**: objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
- **associated symptoms**: sensory, cortical, autonomic, spinal (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
- **history**: family history, developmental history, medications, risk factors, recent/preceding exposures
- **investigations for LMN**: NCS/EMG
- **investigations for UMN**: imaging (brain and/or spinal cord)
- **investigations for suspected myopathy**: muscle biopsy, creatine kinase level, NCS/EMG
- **investigations for suspected neuromuscular junction disorder**: NCS/EMG (with repetitive nerve stimulation and single fiber EMG), antibodies (e.g. acetylcholine receptor antibodies and muscle-specific kinase antibodies for MG, voltage-gated calcium channel antibodies for LEMS)

Differential Diagnosis

- objective muscle weakness; also, differentiate between true muscle weakness vs. fatigue
  - generalized
    - myopathy (proximal > distal weakness)
      - endocrine: hypothyroidism, hyperthyroidism, Cushing's syndrome
      - rheumatologic: dermatomyositis, polymyositis, vasculitis
      - infectious: HIV, influenza
      - other: collagen vascular disorders, corticosteroids, statins, EtOH, electrolyte disorders
  - neuromuscular junction (MG, botulism, LEMS, organophosphate poisoning)
  - polyradiculopathy (infection, malignancy, GBS, CIDP)
  - cachexia
  - localized
    - UMN (vasculitis, abscess, brain tumour, vitamin B_{12} deficiency, MS, stroke)
    - radicular pain (i.e. nerve root)
    - anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic)
    - peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
- no objective muscle weakness
  - chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  - depression
  - deconditioning

Numbness/Altered Sensation

Approach

- positive sensory symptoms: paresthesia/dysesthesia = tingling, pins and needles, prickling, burning, stabbing
- negative sensory symptoms: hypoesthesia/anesthesia = numbness, reduction/absence of feeling
- determine distribution of sensory loss:
  - nerve root vs. peripheral nerve
  - symmetric stocking-glove pattern (indicative of distal symmetric polyneuropathy)
  - dissociated sensory loss: dorsal column (fine touch, proprioception, vibration) vs. spinothalamic tract (pain and temperature)
- investigations: NCS, blood glucose, vitamin B_{12} level, imaging based on associated findings

Differential Diagnosis

- cerebral: stroke, demyelination, tumour
  - symptoms: hemiplegia, aphasia, apraxia
- brainstem: stroke, demyelination, tumour
  - symptoms: diplopia, vertigo, dysarthria, dysphagia, crossed sensory, and/or motor findings
- spinal cord/radiculopathy: cord infarction, tumour, MS, syringomyelia, vitamin B_{12} deficiency, disc lesion
  - symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern), bowel and bladder dysfunction
- neuropathy: focal compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, vitamin B_{12} deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid
  - polyneuropathy (length-dependent neuropathy) will have a stocking-glove distribution of sensory abnormalities
- other: dermatological (e.g. herpes zoster, angioedema), psychiatric disorders (e.g. panic attacks)

Abnormal Gait

Approach

- characterize abnormal gait (posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, difficulty turning, tremor, elaborate/inconsistent movements, standing from sitting)
- full neurological exam
- identify red flags (sudden onset, cerebellar ataxia, paresis (hemi-, para-, quadri-) bowel/bladder incontinence)
- workup based on etiology (blood work, neuroimaging, urgent neurologist referral)

Table 7. Types of Gait Disturbance

Location	Description	Disorder
Visual Loss	Broad based gait with tentative steps	Cataract surgery without lens replacement
Proprioceptive Loss	Sensory ataxia: wide-based with high stepping posture and positive Romberg	Demyelinating neuropathies, paraneoplastic syndrome, tabes dorsalis, MS, compressive myelopathy, vitamin B12 deficiency
Peripheral Vestibular Lesion **1. Acute** **2. Bilateral**	1. Vestibular ataxia 2. Disequilibrium	1. Tumour, trauma, infectious, Ménière's disease 2. Ototoxic drugs
Peripheral Nerve Disorder **1. Foot drop** **2. Lumbosacral radiculopathy**	Steppage gait	Acquired/hereditary peripheral neuropathy, compressive peroneal neuropathy, L4-L5 radiculopathy
Myopathies	Waddling gait: broad based, short stepped gait with pronounced lumbar lordosis, rotation of pelvis	Muscular dystrophy, inflammatory myopathy
Pyramidal/Corticospinal Tract Lesion **1. Unilateral** **2. Bilateral**	Spastic gait: spastic foot drop, circumduction, scissoring of legs or toe walking with bilateral circumduction	Unilateral: stroke (ischemic/hemorrhagic) Bilateral: cervical spondylosis, cerebral palsy, spinal cord tumour, combined spinal cord degeneration, MS, motor neuron disease
Basal Ganglia	1. Parkinsonian gait: short stride length, stooped posture, reduced arm swing 2. Choreic/hemiballistic/dystonic gait	Infarct, PD, progressive supranuclear palsy, MSA, Huntington's, Sydenham's chorea, Wilson's disease, SLE, neuroleptic medications, polycythemia vera, genetic dystonia
Cerebellum	Cerebellar ataxic gait, wide-based without high stepping; veers to side of lesion Alcoholic gait	Primary and secondary neoplasm, toxins (EtOH), vitamin E deficiency, hypothyroid, hypoxia, hypoglycemia, paraneoplastic syndrome, vascular lesion

Cranial Nerve Deficits

- see *Cranial Nerve Exam, N3*

CN I: Olfactory Nerve

Signs and Symptoms

- anosmia (complete loss of smell), hyposmia (partial loss of smell)
- can be unilateral or bilateral, congenital or acquired
- change in smell may be described as a change in taste because of importance of both in flavour

Differential Diagnosis

- nasal obstruction: prevention of odorants from reaching olfactory receptors
  - rhinitis (upper respiratory infection, chronic rhinosinusitis, allergic rhinitis, atrophic rhinitis)
  - nasal mass, foreign body, septal deformity, choanal atresia
- involving olfactory receptor neurons (receptors, cell bodies in epithelium, axons that form CN I)
  - head trauma, smoking, COVID-19
- involving central olfactory structures (olfactory bulb, olfactory tract, primary olfactory cortex)
  - neurological disease (AD, PD, MS), anterior cranial fossa mass (meningioma, aneurysm), intracranial surgery, Kallmann syndrome

CN II: Optic Nerve

- see *Optic Neuropathy, N14*

Kallmann syndrome is a congenital disorder of anosmia and hypogonadotropic hypogonadism

CN III: Oculomotor Nerve

Signs and Symptoms
- vertical and horizontal (oblique) binocular diplopia
- eye position is "down and out" (paralysis of superior rectus, inferior rectus, medial rectus, and inferior oblique, unopposed lateral rectus and superior oblique)
- mydriasis (paralysis of pupillary constrictor)
- ptosis (paralysis of levator palpebrae superioris)

Differential Diagnosis
- peripheral (involving CN III)
  - microvascular ischemia (associated with vascular risk factors, GCA)
  - posterior communicating artery aneurysm, uncal herniation, trauma
  - orbital lesion (associated with optic neuropathy, chemosis, proptosis)
  - cavernous sinus lesion (internal carotid artery aneurysm, meningioma, sinus thrombosis, associated with other CN palsies)
  - demyelination (Miller-Fisher variant of GBS)
- fascicular (involving fascicle in midbrain)
  - demyelination (MS)
- nuclear (involving oculomotor nucleus)
  - midbrain infarction/mass
  - often includes bilateral superior rectus paralysis and ptosis with contralateral pyramidal signs ± mydriasis

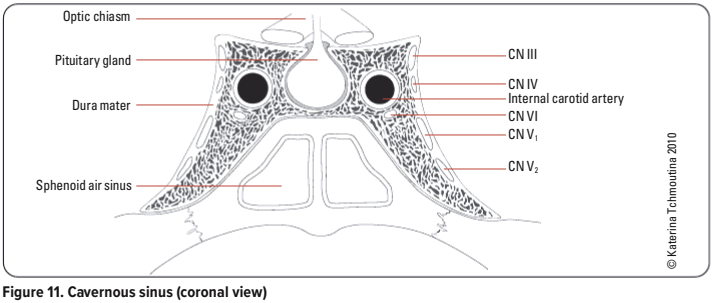


Figure 11. Cavernous sinus (coronal view)

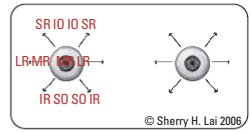


Figure 10. Direction of eye movement to isolate action of extraocular muscle

Parasympathetic axons for pupillary constrictor travel in periphery of CN III
Smaller blood vessels at centre of nerve at greater risk for ischemia
For CN III palsy with reactive pupil, think ischemic cause ("pupil sparing")
For CN III palsy with mydriasis think compressive cause

DDx of CN III Palsy

Ischemic
Compressive (posterior communicating artery aneurysm, uncal herniation, cavernous sinus lesion)
Midbrain lesion (mass, infarction, demyelination)

CN IV: Trochlear Nerve

Signs and Symptoms
- vertical and torsional binocular diplopia
- hypertropia (paralysis of superior oblique, unopposed elevation)
- patient may have contralateral head tilt or describe difficulty going down stairs or reading

Differential Diagnosis
- microvascular ischemia (associated with vascular risk factors, GCA)
- trauma (TBI or surgical)
- cavernous sinus lesion, superior orbital fissure mass (tumour, granuloma)
- demyelination (Miller-Fisher variant of GBS)
- congenital, idiopathic

CN IV is only cranial nerve that exits the brainstem posteriorly
Axons that form CN IV decussate in the midbrain before exiting
Lesions of the trochlear nucleus cause contralateral superior oblique paralysis

CN V: Trigeminal Nerve

- see *Trigeminal Neuralgia, N44*

Signs and Symptoms
- ipsilateral loss of facial sensation and corneal reflex (V1 forms afferent limb)
- ipsilateral weakness of muscles of mastication (V3 only), jaw deviation towards side of weakness

Differential Diagnosis
- pons: infarction, tumour, syringobulbia, demyelination
- peripheral: tumour, aneurysm, chronic meningitis, metastatic infiltration of nerve
- trigeminal ganglion: vestibular schwannoma, meningioma, fracture of middle cranial fossa
- cavernous sinus: internal carotid artery aneurysm, meningioma, sinus thrombosis
- trauma

Jaw deviation is towards the side of a LMN CN V lesion

CN VI: Abducens Nerve

Signs and Symptoms

- horizontal binocular diplopia (worse on lateral gaze towards affected side)
- abduction deficit (paralysis of lateral rectus)
- esotropia (unopposed medial rectus)

Differential Diagnosis

- peripheral (involving CN VI)
  - microvascular ischemia (associated with vascular risk factors, giant cell arteritis)
  - increased or decreased ICP (false localizing sign), trauma, petrous apicitis
  - cavernous sinus lesion (internal carotid artery aneurysm, meningioma, sinus thrombosis, associated with other CN palsies)
  - demyelination (Miller-Fisher variant of GBS)
- fascicular (involving fascicle in pons)
  - demyelination (MS)
- nuclear (involving abducens nucleus)
  - pontine infarction/mass, Duane's syndrome (congenital)
  - presents as lateral gaze palsy due to involvement of internuclear neurons that form pathway to contralateral medial rectus
  - may occur with nuclear facial nerve palsy or corticospinal tract lesion

Distinguishing CN III, IV, and VI Lesions

CN	III	IV	VI
Diplopia	Oblique	Vertical	Horizontal
Eye position	"Down and out"	Hypertropia	Esotropia
Associated Features	Ptosis, mydriasis	Contralateral head tilt	Diplopia worse on lateral gaze

CN VI is vulnerable to increased and decreased ICP, resulting in a false localizing sign

Lesions involving the cavernous sinus can lead to palsies of CN III, IV, VI, V1, and V2 as well as orbital pain and proptosis

CN VII: Facial Nerve

Signs and Symptoms

- unilateral facial weakness (facial droop, flatting of nasolabial fold, inability to wrinkle forehead, and close eyelids)
  - LMN lesion: ipsilateral paralysis
  - UMN lesion: contralateral paralysis with forehead sparing (due to bilateral UMN input to facial motor nucleus for frontalis)
- decreased lacrimation, decreased salivation, hyperacusis (paralysis of stapedius), loss of taste (ageusia) from anterior 2/3 of tongue

Differential Diagnosis

- Bell's palsy (idiopathic): 80-90% of cases (see Otolaryngology, OT22)
- herpes zoster oticus (Ramsay Hunt syndrome)
- otitis media/mastoiditis, sarcoidosis, Lyme meningitis, HIV
- parotid gland disorder, temporal bone fracture

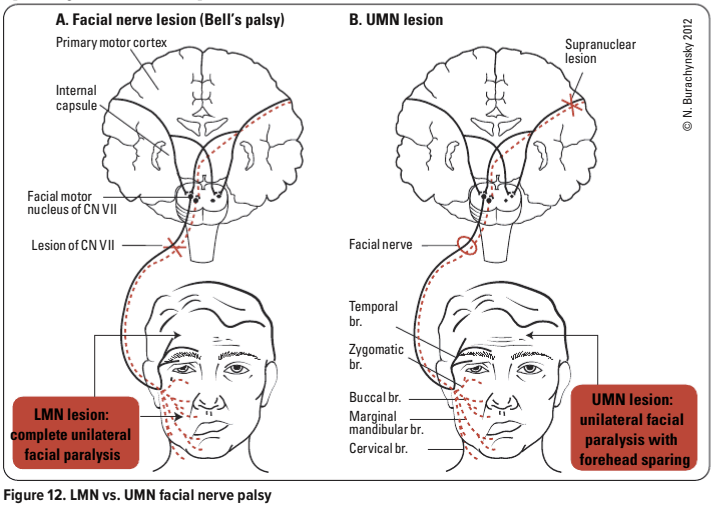


Figure 12. LMN vs. UMN facial nerve palsy

CN VIII: Vestibulocochlear Nerve

- see Otolaryngology, OT9

CN IX: Glossopharyngeal Nerve

Signs and Symptoms
- oropharyngeal dysphagia (paralysis of stylopharyngeus, less severe dysphagia than CN X palsy)
- absent gag reflex (CN IX forms afferent limb)
- loss of taste (ageusia) and sensation from posterior 1/3 of tongue

Glossopharyngeal Neuralgia
- electrical, shock-like, paroxysmal pain from posterior tongue, oropharynx, and ear
- triggers: swallowing, chewing, coughing, talking
- causes: compression (vascular - usually posterior inferior cerebellar artery, neck mass, Eagle syndrome), demyelination, idiopathic
- treated with antiepileptic drugs (carbamazepine), local anesthetic (lidocaine), or surgery (microvascular decompression or surgical ablation of CN IX)

Facial Nerve Branch Memory Aid

"To Zanzibar By Motor Car"
Temporal
Zygomatic
Buccal
Marginal mandibular
Cervical

CN X: Vagus Nerve

Signs and Symptoms
- oropharyngeal dysphagia (paralysis of most muscles of pharynx), for other causes of dysphagia see Gastroenterology, G8
- hoarseness, dysarthria (paralysis of intrinsic muscles of larynx)
- contralateral uvula deviation (paralysis of most muscles of soft palate)
- absent gag reflex (CN X forms efferent limb)

CN X LMN lesions cause contralateral uvula deviation because of paralysis of ipsilateral muscles of soft palate that prevents ipsilateral palatal elevation

When screening for dysphagia and assessing aspiration risk, the presence of a gag reflex is insufficient; the correct screening test is to observe the patient drinking water from a cup while observing for any coughing, choking, or "wetness" of voice

CN XI: Accessory Nerve

Signs and Symptoms
- contralateral head turn weakness (paralysis of sternocleidomastoid)
- ipsilateral shoulder shrug weakness (paralysis of trapezius)
- LMN lesion: ipsilateral paralysis, UMN lesion: contralateral paralysis

CN XI is vulnerable to injury during neck surgery

CN XII: Hypoglossal Nerve

Signs and Symptoms
- tongue weakness (paralysis of ipsilateral muscles of tongue, except palatoglossus)
- tongue deviation to weak side on protrusion (ipsilateral to LMN lesion, contralateral to UMN lesion)
- signs of LMN lesion: atrophy, fasciculations

Neuro-Ophthalmology

Optic Neuropathy

Signs and Symptoms
- vision loss (decreased visual acuity, decreased colour vision, visual field defect)
- RAPD (only if unilateral or asymmetric bilateral optic neuropathy)
- change in appearance of optic disc (optic disc edema, optic disc pallor)

Optic Neuritis
- see *Multiple Sclerosis, N55*

Ischemic Optic Neuropathy
- anterior ischemic optic neuropathy (AION)
  - ischemia of optic nerve head
  - arteritic: most commonly due to GCA
  - non-arteritic: associated with vascular risk factors (DM, hyperlipidemia, HTN)
- posterior ischemic optic neuropathy (PION)
  - ischemia of retrobulbar segment of optic nerve
  - usually perioperative

Other Causes
- traumatic, compressive, toxic, nutritional, hereditary

Optic Atrophy

- non-reversible death of retinal ganglion cells that form the optic nerve
- optic disc pallor on fundoscopic exam, permanent vision loss (decreased visual acuity, visual field defect, decreased colour vision)
- occurs in setting of severe optic neuropathy

Optic Disc Edema

Table 8. Common Causes of Optic Disc Edema

	Optic Neuritis	Papilledema	Anterior Ischemic Optic Neuropathy (AION)	Central Retinal Vein Occlusion (CRVO)
Age	<50 yr	Any	>50 yr but usually >70 yr	>50 yr
Vision	Acute to subacute monocular/ binocular central vision loss (decreased visual acuity and colour vision) with recovery	Late vision loss	Acute, painless unilateral vision loss over h to d with decreased colour vision	Painless unilateral variable vision loss
Symptoms	Pain with eye movement	Symptoms of increased intracranial pressure (headache, nausea, vomiting, focal neurological deficits)	GCA: headache, scalp tenderness, jaw claudication, systemic (weight loss, fatigue, fever)	Acute, painless monocular vision loss
Pupil	RAPD	No RAPD	RAPD	± RAPD
Fundus	Optic disc edema involves optic nerve head, optic disc pallor in chronic stage if severe	Bilateral optic disc edema, retinal hemorrhage, no venous pulsations	Segmental optic disc edema, retinal dot and flame hemorrhages	Optic disc edema, venous engorgement, retinal hemorrhage
Etiologies	MS, neuromyelitis optica, other inflammatory and infectious diseases	Increased ICP see *Table 24, Headaches, N47* IIH if CT/CT venography rules out space-occupying lesion and cerebral venous thrombosis	Arteritic: GCA Non-arteritic: atherosclerosis, DM, hyperlipidemia, HTN	Associated with vascular risk factors, DM, glaucoma, SLE
Investigations	MRI brain and orbits with gadolinium	Emergent CT with CT venography, LP if CT normal, to measure CSF opening pressure	CBC, ESR, C-reactive protein temporal artery biopsy, MRI orbits with gadolinium	Fluorescein angiography, thrombophilia workup if no cause identified (younger patients)
Treatment	High-dose IV or PO corticosteroids (accelerates recovery of vision, does not improve long-term outcome)	Treat underlying cause of increased ICP	Arteritic: corticosteroids Non-arteritic: no proven treatment	Optimize risk factors, reduce intraocular pressure, ± laser, ± vascular endothelial growth factor) inhibitors

If diagnosis of GCA is suspected, do not wait for temporal artery biopsy; begin treatment with corticosteroids immediately

Visual Field Defects

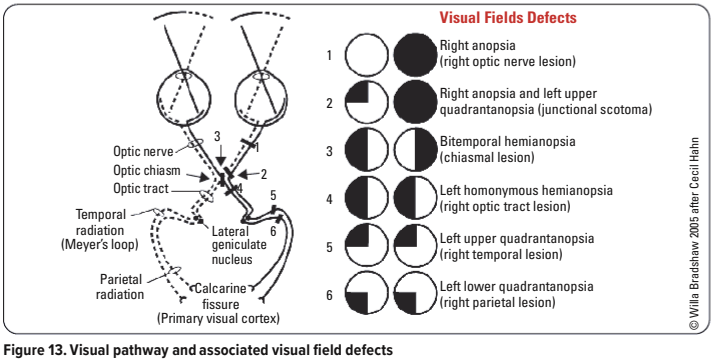


Figure 13. Visual pathway and associated visual field defects

DDx of Bitemporal Hemianopsia by Age
Children: craniopharyngioma
20-50 yr: pituitary adenoma
>60 yr: meningioma

In homonymous hemianopsia, more congruent deficits are caused by more posterior lesions; macular sparing may occur with occipital lesions

Lesion of the frontal eye field (FEF) (i.e. stroke, tumour) causes eye deviation towards the side of the lesion

Overactivation of the FEF (i.e. seizure) causes eye deviation away from the side of overactivation

Lesion of the paramedian pontine reticular formation (PPRF) (i.e. stroke, tumour) causes eye deviation away from the side of the lesion

Amaurosis Fugax

- see Ophthalmology, OP36 and *Stroke, N51*

Pupil Abnormalities

- see Ophthalmology, OP29

Eye Movement Disorders

Internuclear Ophthalmoplegia

Pathophysiology
- caused by lesion of medial longitudinal fasciculus (MLF) that impairs horizontal gaze pathway
- MLF connects abducens nucleus in pons to contralateral medial rectus subnucleus of oculomotor nucleus in midbrain

Signs and Symptoms
- horizontal binocular diplopia (worse on lateral gaze towards opposite side of lesion)
- adduction deficit in eye ipsilateral to lesion
- horizontal abducting nystagmus in eye contralateral to lesion
- can differentiate from medial rectus denervation (i.e. CN III palsy) by testing convergence since it is separate from horizontal gaze pathway
- can be bilateral (especially MS)

Etiology
- demyelination of MLF (i.e. MS), brainstem infarction/mass

Investigation
- MRI brain

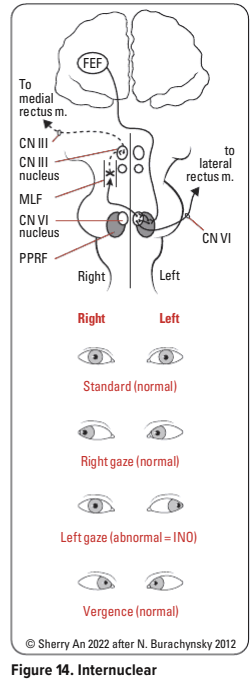


Figure 14. Internuclear ophthalmoplegia

Diplopia

Definition
- visual symptom characterized by the perception of two images of a single object
- also called double vision

Classification
- monocular: diplopia remains when unaffected eye is closed
- binocular: diplopia disappears when either eye is closed
- based on where the two images are relative to each other, diplopia can be described as vertical, horizontal or oblique

Etiology – Monocular
- benign optical problem (refractive error, cataract, corneal abnormality, dry eye) or functional

Etiology – Binocular
- caused by ocular misalignment
- classification of cause
  - muscle: extraocular muscle restriction/entrapment (orbital fracture, orbital mass, Graves' ophthalmopathy), myopathy
  - neuromuscular junction: MG, LEMS
  - nerve: CN III, IV, VI palsy
  - brain: internuclear ophthalmoplegia, stroke, Wernicke's encephalopathy

Approach
- monocular or binocular
- vertical, horizontal or oblique
- worse in specific direction of gaze
- onset (acute, chronic), progression
- corrective head positions
- associated symptoms (ptosis, miosis/mydriasis, symptoms of GCA, fatigable weakness)

Diplopia worse at the end of the day suggests MG (i.e. variable and fatigable), usually with associated ptosis

Nystgmus

Definition
- rapid, involuntary, small-amplitude eye movements that are rhythmic in nature

Classification
- based on axis of movement (vertical, horizontal, torsional)
- based on movement type
  - jerk: slow drift in one direction (slow phase) followed by a fast corrective movement in the opposite direction (fast phase), direction of nystagmus is named after fast phase, fast phase may occur in one direction or multiple directions (unidirectional, bidirectional, multidirectional)
  - pendular: smooth, sinusoidal pattern without a fast phase

- based on cause
  - congenital or acquired, physiological or pathological (peripheral or central)

Table 9. Nystagmus Features

Characteristic	Peripheral (Vestibular)	Central (Brainstem)
Lesion Location	Peripheral vestibular system (semicircular canals, vestibulocochlear nerve)	CNS (usually cerebellum, brainstem or visual pathway)
Nystagmus Features	Often horizontal and torsional components, unidirectional, fast phase away from lesion	Often purely vertical, horizontal or torsional, can be bidirectional or multidirectional
Gaze Fixation	Decreases nystagmus	No effect on nystagmus
Vertigo	Severe	Mild
Auditory Symptoms	Common	Rare
Other Neurological Signs	Rare	Common
Adaptation	Within days	Often persists
Causes	Benign paroxysmal positional vertigo (BPPV), vestibular neuritis, Ménière's disease, trauma ototoxic medications	MS, stroke, neoplastic, paraneoplastic, medications

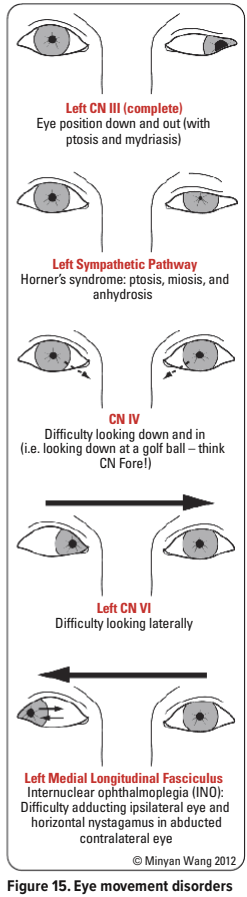

Left CN III (complete)
Eye position down and out (with ptosis and mydriasis)
Left Sympathetic Pathway
Horner's syndrome: ptosis, miosis, and anhydrosis
CN IV
Difficulty looking down and in (i.e. looking down at a golf ball – think CN Fore!)
Left CN VI
Difficulty looking laterally
Left Medial Longitudinal Fasciculus
Internuclear ophthalmoplegia (INO): Difficulty adducting ipsilateral eye and horizontal nystagamus in abducted contralateral eye
© Minyan Wang 2012

Figure 15. Eye movement disorders and Horner's syndrome

Nutritional Deficiencies and Toxic Injuries

- sufficient nutritional intake is required for optimal functioning of the nervous system; deficiencies in the following nutrients may result in CNS and PNS abnormalities (potential neurological symptoms are provided)

Table 10. Nutritional Deficiency Features and Management

Vitamin Deficiency	Neurological Clinical Manifestation	Investigation	Treatment*
Vitamin B_{12}	Paresthesias and sensory ataxia are the most common initial symptoms Myelopathy (subacute combined degeneration), peripheral neuropathy Neuropsychiatric symptoms: memory impairment, change in personality and mood, delirium, and psychosis Optic neuropathy	CBC and blood smear Serum cobalamin Serum methylmalonic acid Serum homocysteine Intrinsic factor antibodies	Vitamin B_{12} 1000 µg IM once weekly for 4 wk then 1000 µg PO daily or IM monthly thereafter
Folate	May be clinically indistinguishable from vitamin B_{12} deficiency Myelopathy, peripheral neuropathy Neuropsychiatric symptoms Neural tube defects (in fetus	Serum folate Homocysteine	Folic acid 1-5 mg PO TID initially, then 1 mg PO once daily thereafter
Copper	Myelopathy, myeloneuropathy, sensory ataxia, spastic gait (similar to vitamin B_{12} deficiency) Severe sensory loss	Serum copper and ceruloplasmin Urinary copper MRI spine; EMG/NCS	Discontinue zinc; copper 8 mg/d PO daily for 1 wk, then 4 mg PO daily for 2 wk, then 2 mg PO daily thereafter
Vitamin E	Ophthalmoplegia, retinopathy, spinocerebellar syndrome with peripheral neuropathy (with signs of cerebellar ataxia), psychomotor impairment	Serum vitamin E Ratio serum vitamin E to sum of cholesterol and triglycerides; EMG/NCS	Vitamin E 2200 mg/kg/d PO or IM
Thiamine (Vitamin B_1)	Three manifestations include: beriberi (dry and wet), infantile beriberi, Wernicke-Korsakoff syndrome, see *Cerebellar Disorders, N36*	Clinical diagnosis MRI brain	Thiamine 200 mg IV TID, followed by 10 mg PO once daily until nutritional status stable If suspected Wernicke-Korsakoff syndrome: 500 mg TID for 2 d, followed by 250 mg IV or IM for 2 d
Pyridoxine (Vitamin B_6)	Painful sensorimotor peripheral neuropathy, intractable epilepsy in infants, confusion	Serum pyridoxal phosphate EMG/NCS EEG in infants and children	Pyridoxine 50-100 mg PO once daily
Niacin (Vitamin B_3)	Pellagra: encephalopathy, dementia, and peripheral neuropathy	Urinary nicotinamide mononucleotide (NMN) and nuclear matrix protein (NMP) tests Niacin index	Nicotinic acid 25-50 mg PO daily or IM once daily. When supplementing, be aware of "niacin flush" in some patients

- also consider occupational neurotoxic syndromes secondary to exposure to pesticides, solvents, and metals. Encephalopathy, extrapyramidal features, neurodegenerative diseases, and peripheral neuropathy are commonly encountered. Onset and progression of neurological diseases should be temporally related to neurotoxin exposure. Main toxins associated with neurotoxicity are listed on *Table 11, N18*

Table 11. Selected Occupational Neurotoxic Syndromes

Toxin	Associated Occupations	Characteristic Neurological Findings
Organic Solvents	Printer, spray painters, industrial cleaners, paint or glue manufacturers, graphic industry, electronic industry, plastic industry	Acutely, may present as nausea, headache, concentration difficulty Long-term exposure may lead to "chronic solvent-induced encephalopathy" (characterized by mild-to-severe cognitive impairment), seizures, death
Pesticides (e.g. insecticides, fungicides, rodenticides, fumigants, herbicides)	Agricultural work, pesticide manufacturing and formulating, highway and railway workers, green house, forestry, and nursery workers	May increase the risk of PD
Heavy Metals (e.g. lead, mercury, manganese, aluminum, arsenic, tin, thallium)	Battery and metal production (e.g. solder, pipes), chemical and electronic application industries, steel manufacturing, welders, alloy workers, transportation, packaging, construction	**Lead:** headache, difficulty concentrating, deficits in short-term memory, delayed/reversed development, permanent learning disabilities, peripheral neuropathy (commonly presenting with radial neuropathy resulting in wrist drop), seizures, coma, delirium, death from encephalopathy (rare) **Mercury:** psychiatric symptoms, ataxia, tremor, visual loss, hearing loss, tiredness, memory disturbances, peripheral neuropathy **Manganese:** psychiatric symptoms, hallucinations ("manganese madness"), extrapyramidal features, headache, dystonia, parkinsonism (manganism) **Aluminum:** implicated in AD and Down's syndrome pathogenesis **Arsenic:** peripheral neuropathy, encephalopathy, sleeplessness/sleepiness, irritability, headache, spasms and fatigue in appendicular muscles, peripheral neuropathy **Thallium:** ataxia, seizures, motor neuropathy, brain edema **Tin:** mental status changes with persistent neuropsychological abnormalities
Gases (e.g. carbon dioxide, nitrous oxide, formaldehyde)	Anesthesia, disinfection, manufacture of illuminating gas and water-gas	Cognitive/behavioural and emotional symptoms, parkinsonian syndromes Nitrous oxide misuse may result in a functional vitamin B12 deficiency and thus symptoms of subacute combined degeneration

Neurologic Complications due to Toxic Injuries Related to Bariatric Surgery

- deficiencies of both fat- and water-soluble vitamins may occur following malabsorptive bariatric surgery
- patients who have undergone malabsorptive surgery should be monitored for late metabolic complications (e.g. B_{12} and copper deficiency) and neurological manifestations (e.g. peripheral neuropathy)

Seizure Disorders and Epilepsy

Seizure

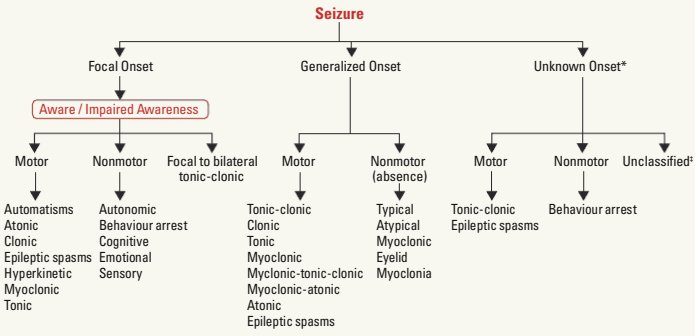
Definitions

- seizure: transient signs and/or symptoms due to abnormal hyper-synchronization of neurons
  - precipitating factors (acute brain insult) such as: EtOH and illicit drug use/withdrawal; brain injury/abnormality (tumour, trauma, vascular); CNS infection; fever (children); metabolic (hypoglycemia, electrolyte abnormalities, liver/renal failure); medications; or genetic cause
- epilepsy: enduring predisposition to generate epileptic seizures, with its associated neurobiologic, cognitive, psychological, and social consequences
  - diagnosis of epilepsy requires:
    1. at least two unprovoked seizures >24 h apart
    2. one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (≥60%) of two unprovoked seizures, occurring over the next 10 yr
    3. diagnosis of an epilepsy syndrome
  - etiologies: genetic; structural (e.g. prior stroke, tumour, meningo/encephalitis, perinatal insult, vascular malformation, malformation of cortical development, neurodegenerative); or unknown

Stroke is the most common cause of late-onset (>50 yr) seizures, accounting for 50-80% of cases

Seizures and Dementia
Neurodegenerative diseases can underlie seizures. Conversely, seizures can be a cause of dementia

Classification



*Unknown Onset may be reclassified into focal or generalized onset with further information or future observed seizures
‡ Unclassified comprises both seizures with patterns that do not fit other categories or lack information

Figure 16. International League Against Epilepsy (ILAE) 2017 seizure classification

Clinical Features

- **focal (partial) seizures**
  - focal can secondarily generalize or remain focal
  - focal without impaired awareness (i.e. "simple partial seizures") → focal with impaired awareness (i.e. "complex partial seizures") → secondarily generalized seizures
  - **focal aware (formerly simple partial)**
    - motor: dystonic posturing, clonic movements, forceful turning of eyes and/or head, focal muscle rigidity/jerking ± Jacksonian march (spreading to adjacent muscle groups)
    - sensory: unusual sensations affecting vision, hearing, smell, taste or touch
    - autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
  - **focal impaired awareness (formerly complex partial)**
    - classic complex seizure is characterized by automatisms such as chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing, and other stereotypic movements
    - other forms: dysphasic, dysmnesic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness
- **generalized seizures**
  - **absence (petit mal):** usually seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - **clonic**: whole body repetitive rhythmic jerking movements
  - **tonic**: whole body muscle rigidity in flexion or extension
  - **tonic-clonic (grand mal)**
    - may have prodrome of unease or irritability hours to days before
    - tonic ictal phase: muscle rigidity
    - clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence
    - post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated creatine kinase lasting hours, may have focal paralysis ('Todd's paralysis)
  - **myoclonic**: sporadic contractions localized to muscle groups of one or more limbs
  - **atonic**: loss of muscle tone leading to drop attack

Temporal lobe seizures are suggested by an aura of fear, olfactory or gustatory hallucinations, and visceral or déjà vu sensations
Frontoparietal cortex seizures are suggested by contralateral focal sensory or motor phenomena

Antiepileptic Drug Monotherapy for Epilepsy: A Network Meta-Analysis of Individual Participant Data
Cochrane DB Syst Rev 2017;CD011412
Purpose: To compare the time to withdrawal of treatment, time to remission, and time to first seizure of 10 antiepileptic drug treatments for adults and children with partial onset seizures
Methods: Articles were identified from Cochrane Epilepsy's Specialised Register, CENTRAL, MEDLINE, SCOPUS, and two clinical trial registers. Individual patient data was identified for network-meta analysis
Results: Carbamazepine and lamotrigine are suitable first-line treatments for partial onset seizures with levetiracetam as a suitable alternative. Evidence supports sodium valproate as first-line treatment for generalized tonic-clonic seizures with lamotrigine and levetiracetam as suitable alternatives, particularly for females of child-bearing age

DDx of Convulsions
Syncope, psychogenic non-epileptic seizures, hyperventilation, panic disorder, TIA, hypoglycemia, movement disorder, alcoholic blackouts, migraines (confusional, vertebrobasilar), narcolepsy (cataplexy)

Table 12. Classic Factors Differentiating Seizure, Syncope and Pseudoseizure

Characteristic	Seizure	Syncope	Dissociative/Functional Seizures
Timing	Day or night (especially from sleep)	Day	Day, other people present
Onset	Sudden, in any position	Gradual, upright position (not recumbent)	Provoked by emotional disturbance or suggestion
Early Symptoms or Signs	Possible specific aura	Lightheadedness, pallor, diaphoresis, tunnel vision	Variable
Duration	Brief or prolonged	Brief	Often prolonged
Incontinence	Common	Possible but rare	Rare
Post-Ictal	Confusion, aphasia, Todd's paresis, fatigue	No	Variable, often none
Motor Activity	Synchronous, stereotypic, automatisms (common in complex partial), lateral tongue biting, eyes open or eyes rolled back	Occasional brief tonic stiffening, can have "convulsive syncope"	Prolonged episodes, opisthotonos, eye closure, irregular limb movements, shaking head, pelvic thrust, crying, tongue biting at the tip
Injury	Common	Rare unless from fall	Rare
EEG	Usually abnormal ± interictal discharges	Normal	Normal

*Pseudoseizures do not rule out seizures (not uncommon to have both)

Note that seizures originating in the frontal lobes may look like psychogenic non-epileptic spells due to an abundance of repetitive hyperkinetic movements; they often occur during sleep

By law, the Ministry of Transportation in most provinces must be contacted for all patients who have had a seizure, patients will have their license suspended until seizure free for 6 mo, commercial drivers face a longer wait

EEG findings suggestive of predisposition to epilepsy: spike and wave discharges, polyspike and wave discharges, spike-wave complex discharges

EEG has a 17% sensitivity and 95% specificity after first unprovoked seizure, sensitivity increases to 51% if EEG is performed within 24 h
If the first routine EEG is normal, a sleep-deprived sleep EEG should be considered to increase the likelihood of detecting an abnormality

- alcoholic withdrawal seizures may occur up to 2 d from the last exposure to EtOH (see Emergency Medicine, ER54)

Investigations
- CBC, electrolytes, Ca^{2+}, Mg^{2+}, PO_4^{3-}, fasting blood glucose, Cr, liver enzymes, creatine kinase, prolactin
- toxicology screen, EtOH level, ASM level (if applicable)
- CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
  (Note: Neuroimaging may be normal in up to 90% of cases following the first unprovoked seizure)
- LP (if fever or meningismus)
- EEG (Note: EEG is specific but not sensitive)

Treatment
- avoid precipitating factors
- prognosis: risk of seizure recurrence increases with the number of unprovoked seizures at initial presentation, abnormal EEG, and presence of a neurological disorder
- indications for ASM: EEG with epileptiform activity, prior brain injury (organic brain disease, prior head injury, or CNS infection), abnormal neurologic examination or neuroimaging findings, nocturnal seizure, recurrent unprovoked seizure
- psychosocial issues: stigma of seizures, education of patient and family, status of driver's license, pregnancy issues
- safety issues: driving, operating heavy machinery, bathing, swimming alone
- appropriate follow-up; refer for evaluation for possible surgical treatment if focal and refractory

Status Epilepticus

- **definition**: unremitting seizure or successive seizures without return to baseline state of >5 min
- **complications**: anoxia, cerebral ischemia and cerebral edema, MI, arrhythmias, cardiac arrest, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)
- **initial measures**: ABCs, vitals, monitors, capillary glucose (STAT), ECG, nasal O_2, IV normal saline, IV glucose, IV thiamine, arterial blood gas (if respiratory distress/cyanotic)
- **blood work**: electrolytes, Ca^{2+}, Mg^{2+}, PO_4^{3-}, glucose, CBC, toxicology screen, EtOH level, ASM levels
- focused history: onset, past history of seizures, drug and EtOH ingestion, past medical history, associated symptoms, witnesses/collateral history
- **physical exam (once seizures controlled):** LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (rule out injuries)
- **post-treatment stabilization**: CT head, EEG, Foley catheter to monitor urine output, urine toxicology screen, monitor for rhabdomyolysis, and IV fluids to maintain normal cerebral perfusion pressure

Medical Emergency: Status epilepticus can cause irreversible brain damage without treatment

The most common causes of status epilepticus in adults are failure to take ASM, remote symptomatic causes, and stroke
Despite being a common cause of seizures, EtOH withdrawal is a rare cause of status epilepticus

Consider non-convulsive status epilepticus in a patient who has a persistent decreased level of awareness >20 min after a generalized seizure; order an EEG if unsure

Antiseizure Medications
- focal and most generalized seizures
  - valproate (Depakene®), lamotrigine (Lamictal®), levetiracetam (Keppra®), topiramate (Topamax®), phenobarbital (Phenobarb®), primidone, zonisamide, rufinamide (Banzel®), felbamate, benzodiazepines
- primarily focal seizures (± 2° generalization)
  - carbamazepine (Tegretol®), phenytoin (Dilantin®), gabapentin (Neurontin®), lacosamide (Vimpat®), oxcarbazepine (Trileptal®), eslicarbazepine acetate (Aptiom®), pregabalin (Lyrica®), tiagabine (Gabitril®), vigabatrin (Sabril®)
- absence seizure: ethosuximide (Zarontin®)

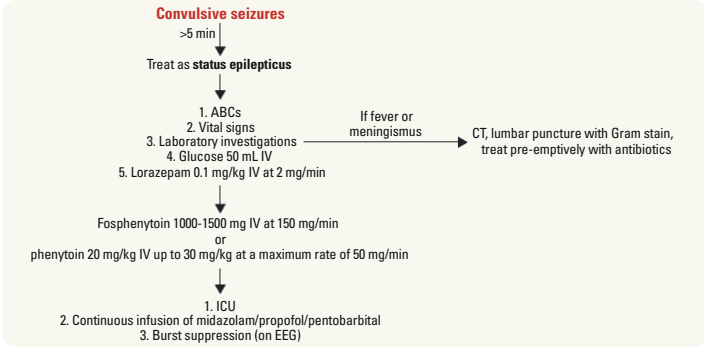

Convulsive seizures
>5 min
Treat as status epilepticus
1. ABCs
2. Vital signs
3. Laboratory investigations
4. Glucose 50 mL IV
5. Lorazepam 0.1 mg/kg IV at 2 mg/min
If fever or meningismus
CT, lumbar puncture with Gram stain, treat pre-emptively with antibiotics
Fosphenytoin 1000-1500 mg IV at 150 mg/min
or
phenytoin 20 mg/kg IV up to 30 mg/kg at a maximum rate of 50 mg/min
1. ICU
2. Continuous infusion of midazolam/propofol/pentobarbital
3. Burst suppression (on EEG)

Figure 17. Status epilepticus treatment algorithm

Complex partial status epilepticus can resemble schizophrenia or psychotic depression

Teratogenicity of anticonvulsants includes neural tube defects, cleft palate, urogenital malformations, and heart defects. Advise patient planning pregnancy to take 1-4 mg/d of folic acid. Optimize AEDs with lowest possible dose associated with good seizure control, preferably monotherapy if possible. The risk of fetal malformations with AEDs is 2x the general population; highest risk associated with valproic acid and/or 2+ concurrent AEDs. Consider pre-conception AED levels if patient is well-controlled, monthly serum levels during pregnancy, and titrate AED to maintain pre-conception serum levels. Refer to high-risk OB for intrapartum fetal screening

Behavioural Neurology

- see Psychiatry, PS23

Acute Confusional State/Delirium

Table 13. Selected Causes of Acute Confusion

	Etiology	Key Clinical Features	Investigations
Vascular	SAH	Thunderclap H/A, increased ICP, meningismus, loss of consciousness	CT, LP Angiography if CT and LP negative
	Stroke/TIA (ischemic or hemorrhagic)	Focal neurological signs	CT, MRI
Infectious	Meningitis	Fever, H/A, nausea, photophobia, meningismus	CT, LP
	Encephalitis	Fever, H/A, ± seizure Focal neurological signs	CT, LP MRI
	Abscess	Increased ICP Focal neurological signs	CT with contrast (often ring enhancing lesion)
Traumatic	Diffuse axonal shear, epidural hematoma, subdural hematoma	Trauma Hx Increased ICP Focal neurological signs	CT MRI
Autoimmune	Acute CNS vasculitis	Skin rash, active joints	ANA, ANCA, RF MRI Angiography
	Paraneoplastic or autoimmune encephalitis (anti-NMDA-R)	Onset: psychiatric features, memory loss, seizures Delayed: movement disorder, and changes in BP, HR, and temperature	Serum and CSF (test for presence of antibodies), search for primary neoplasm
Neoplastic	Primary or secondary CNS neoplasm	Increased ICP Focal neurological signs Papilledema	CT MRI Search for primary neoplasm if metastatic disease
Seizure	Focal seizure with impaired awareness, non-convulsive status epilepticus, post-ictal confusion	See *Seizure Disorders and Epilepsy, N18*	EEG CT or MRI Workup for seizure triggers
Primary Psychiatric	Psychotic, mood, and anxiety disorder	No organic signs or symptoms	No specific tests
Other	Illicit drug use (e.g. cocaine)	Chest pain, cough with black sputum, new-onset seizure, HTN, increased ICP, dyspnea	Vital signs Serum chemistry and electrolyte analysis Serum and urine toxicology screen
	Medications (e.g. anticholinergic side effects, benzodiazepines)	Flushing, dry skin and mucous membranes, mydriasis with loss of accommodation	Serum chemistry and electrolyte analysis
	Neuroleptic Malignant Syndrome	Antipsychotic medication use Muscle rigidity Hyperthermia Autonomic instability	Serum chemistry and electrolyte analysis

Delirium is a medical emergency carrying significant risk of morbidity and mortality. It is diagnosed using the Confusion Assessment Method when feature 1 AND 2 as well as feature 3 OR 4 are present:

- **Feature 1:** acute onset and fluctuating course
- **Feature 2:** inattention
- **Feature 3:** disorganized thinking
- **Feature 4:** altered LOC

Mild Neurocognitive Disorder (Mild Cognitive Impairment)

Definition
- change in cognition
  - Impairment in one or more cognitive domains (amnestic vs. non-amnestic)
  - preservation of independence or minimal impairment in ADLs and IADLs
  - Not meeting criteria for major NCD

Epidemiology
- mild NCD: 2-10% at age 65 and 5-25% by age 85

Risk Factors
- non-modifiable: age, history of stroke or heart disease, and apolipoprotein E (APOE) ε4 genotype
- modifiable: educational level and vascular risk factors (e.g. HTN, DM, obesity)

Clinical Features
- cognitive impairment with different subtypes
  - single domain vs. multiple domains (e.g. memory, visual spatial function, attention, executive function, language)
  - amnestic (memory impairment) vs. non-amnestic (memory function preserved)
  - amnestic subtype is the most common and most associated with AD pathology
  - important to ascertain that memory complaints represent change from baseline
- neuropsychiatric symptoms: depression (50%), irritability, anxiety, aggression, and apathy

Investigations
- establish a baseline for follow-up with validated cognitive screening tool
- clinical interview with patient and caregivers, including family history
- neuropsychological testing
  - MMSE (not sensitive to early cognitive change) or MoCA (more sensitive); should be done in conjunction with a history and neurological exam or with other neurocognitive tests
  - if abnormal, follow-up in one year to monitor cognitive and functional decline
- neuroimaging
  - role uncertain; non-contrast CT head often ordered to evaluate for structural abnormalities (CVD, subdural hematoma, NPH, or mass lesion); MRI is helpful to establish baseline and to look for other possible reversible causes of cognitive impairment
- other testing to exclude treatable conditions (e.g. vitamin B12 deficiency, hypothyroidism, seizures, autoimmune encephalitis) and underlying psychiatric conditions (e.g. depression)

Treatment
- non-pharmacologic management: exercise training for 6 mo is likely to improve cognition; insufficient evidence to support or refute cognitive intervention, it may improve outcome on select cognitive measures
- pharmacologic management: monitoring and management of HTN and other vascular risk factors is recommended
- no evidence for cholinesterase inhibitors, anti-inflammatory agents

Prognosis
- development of major NCD for age ≥65 is 14.9% after 2 yr
- relative risk of major NCD is 3.3 after 2-5 yr

Prevalence of Depression in Patients with Mild Cognitive Impairment: A Systematic Review and Meta-Analysis
JAMA Psychiatry 2017;74:58-67
Purpose: To estimate the prevalence of depression in individuals with mild cognitive impairment.
Methods: Review of articles with patients with mild cognitive impairment as a primary study group, reported depression/depressive symptoms using a validated tool, and reported the prevalence of depression in patients with mild cognitive impairment.
Results: Pooled prevalence of depression patients with mild cognitive impairment was 32% (95% CI 27-37%). Prevalence in community-based populations (25%, 95% CI 19-30) was significantly lower than clinic-based populations (40%, 95% CI 32-48).
Conclusions: Prevalence of depression in patients with mild cognitive impairment is high.

Major Neurocognitive Disorder (formerly Dementia)

- see Psychiatry, PS24

Definition
- progressive decline in cognitive function with impairment in ADLs/IADLs (e.g. shopping, food preparation, finances, medication management)
- diagnosis of major NCD requires presence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on:
  a) concern of the individual or a knowledgeable informant AND
  b) substantial impairment in cognitive performance either documented by standardized neuropsychological testing or quantified clinical assessment

Epidemiology
- major NCD: 1-2% at age 65 and reaching as high as 30% by age 85
- major NCD due to AD is uncommon before age 60
- major NCD due to frontotemporal lobar degeneration has an earlier onset and represents a progressively smaller fraction of all NCDs with increasing age

Etiology *(see Table 14, N23)*
- reversible causes: EtOH (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metal toxicity, hepatic or renal failure, vitamin B12 deficiency, glucose, cortisol, thyroid dysfunction, NPH, depression (pseudodementia), intracranial tumour, subdural hematoma, and hypercalcemia
- must rule out delirium

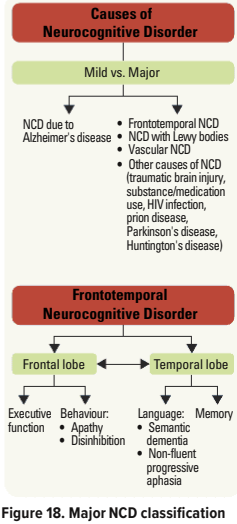


Figure 18. Major NCD classification

History
- "geriatric giants"
  - confusion/incontinence/falls
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects, driving)
  - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
  - polypharmacy and compliance (sedative hypnotics, antipsychotics, antidepressants, anticholinergics)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS, head trauma history
- EtOH, smoking
- collateral history
- FHx

Physical Exam
- BP
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings
- general physical exam with focus on CVD, patient-specific risk factors, and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

Investigations
- rule out reversible causes
  - CBC (note MCV for evidence of alcohol use and vitamin B_{12} deficiency), glucose, TSH, vitamin B_{12}, RBC folate
  - electrolytes, LFTs, renal function, lipids, serum calcium
  - CT head, MRI as indicated, SPECT (optional)
  - as clinically indicated: VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
  - failure to cope, fitness to drive, caregiver capacity and wellbeing, power of attorney, legal will, advanced medical directives, patient and caregiver safety

Table 14. Selected Causes of Major NCD (Dementia)

Etiology	Key Clinical Features	Investigations
PRIMARY DEGENERATIVE		
Alzheimer's disease	Memory impairment Aphasia, apraxia, agnosia	CT or MRI, FDG-PET or SPECT
Dementia with Lewy bodies	Visual hallucinations Parkinsonism Fluctuating cognition REM sleep behaviour disorder Severe neuroleptic sensitivity	CT or MRI, SPECT
Frontotemporal dementia (e.g. Pick's disease)	Behavioural presentation: disinhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared Language presentation: progressive non-fluent aphasia, semantic dementia	CT or MRI, SPECT
Huntington's disease	Chorea Neuropsychiatric symptoms	Genetic testing
VASCULAR		
Vascular cognitive impairment (previously Multi-infarct dementia)	Bradyphrenia without features of parkinsonism (slow thinking, slow rate of learning, slow gait) Dysexecutive syndrome May be abrupt onset Stepwise deterioration is classic but progressive deterioration is most common	CT or MRI, SPECT
CNS vasculitis	Systemic signs and symptoms of vasculitis	ANA; ANCA; RF CT or MRI Angiography
INFECTIOUS		
Chronic meningitis	Fever, H/A, nausea (triad often absent in cases of chronic meningitis) Meningismus Localizing neurological deficits	CT,MRI, LP
Chronic encephalitis	Fever, H/A	CT or MRI
Chronic abscess	Increased ICP Localizing neurological deficits	CT with contrast, MRI
HIV	See Infectious Diseases, ID27	HIV serology
Creutzfeldt-Jakob disease	Rapidly progressive, myoclonus, akinetic mutism, parkinsonism, or cortical symptoms	EEG, CT or MRI, LP
Syphilis	Ataxia, myoclonus, tabes dorsalis	LP, CT, or MRI VDRL
TRAUMATIC		
Diffuse axonal shear, epidural hematoma, subdural hematoma	Trauma Hx Increased ICP, papilledema Localizing neurological signs	CT, MRI

Sensitivity and Specificity

Tool	Sensitivity	Specificity
MMSE	87%	82%
Clinical Judgment	85%	82%
DSM IV	76%	80%

Vitamin B_{12} Deficiency Symptoms
- Macrocytic anemia, pallor, SOB, fatigue, chest pain, palpitations
- Confusion or change in mental status (if advanced)
- Decreased vibration sense
- Distal numbness and paresthesia
- Weakness with UMN findings
- Diarrhea, anorexia

Major NCD Considerations for Management

ABCDs
Affective disorders, ADLs
Behavioural problems
Caretaker, Cognitive medications and stimulation
Directives, Driving
Sensory enhancement (glasses/hearing aids)

Most common causes of rapidly progressive neurodegenerative dementia are CJD, frontotemporal lobar dementia, tauopathies, diffuse Lewy body disease, and AD

Features of Early Major NCD vs. Normal Aging

Early Signs of Major NCD	Normal Aging
Forgetting the names of close relations	Forgetting the names of acquaintances
Increased frequency of forgetting	Briefly forgetting part of an experience
Repeating phrases/ stories in the same conversation	Not putting away things properly
Unpredictable mood changes	Mood changes in response to appropriate causes
Decreased interest in activities and difficulty making choices	Changes in usual interests

Table 14. Selected Causes of Major NCD (Dementia)

Etiology	Key Clinical Features	Investigations
RHEUMATOLOGIC		
SLE	See Rheumatology, RH11	MRI ANA, anti-dsDNA
NEOPLASTIC		
Primary or secondary brain tumour (metastasis), paraneoplastic encephalitis	Increased ICP Localizing neurological signs Systemic symptoms of cancer	CT with contrast MRI Paraneoplastic antibodies
OTHER		
Normal pressure hydrocephalus	Gait disturbances Urinary incontinence See Neurosurgery, NS9	CT or MRI, large volume LP

Cholinesterase Inhibitors for Dementia with Lewy Bodies (DLB), Parkinson's Disease Dementia (PDD) and Cognitive Impairment in Parkinson's Disease (CIND-PD)
Cochrane DB Syst Rev 2012;3:CD006504
Purpose: To assess the efficacy of treatment with cholinesterase inhibitors in DLB, PDD, and CIND-PD.
Methods: Review of articles from databases including MEDLINE, EMBASE, PsychINFO, and CINAHL.
Results: The six trials (n=1236) included demonstrated therapeutic benefit of cholinesterase inhibitors for global assessment, cognitive function, behavioural disturbance, and activities of daily living. Cholinesterase inhibitors were associated with increased adverse events (OR 1.64) and drop out (OR 1.94). Adverse events were more common with rivastigmine but not with donepezil. Fewer deaths occurred in the treatment group (OR 0.28).
Conclusion: Current evidence supports use of cholinesterase inhibitors for patients with PDD, but its role in DLB and CIND-PD is still unclear.

Major or Mild Neurocognitive Dementia due to Alzheimer's Disease

- see Psychiatry, PS23

Definition

- beyond criterion for NCD, the core features of AD include an insidious onset and gradual progression of cognitive and behavioural symptoms
- typical presentation: amnestic
  - mild phase: impairment in memory and learning sometimes accompanied with deficits in executive function
  - moderate-severe phase: visuoconstructional/perceptual-motor ability and language may also be impaired
  - social cognition tends to be preserved until late in the course of the disease
- atypical nonamnestic presentation (one of the following):
  1. language: aphasia, word-finding difficulty
  2. visuospatial: object agnosia, prosopagnosia, simultanagnosia, alexia, limb apraxia
  3. executive: reasoning, judgment, and problem-solving are affected

4 As and one D of AD
Anterograde amnesia
Aphasia
Apraxia
Agnosia
Disturbance in executive function
(Anterograde amnesia plus at least one of the other features is required for AD diagnosis)

Pathophysiology

- genetic factors
  - minority (<1%) of AD cases are familial (autosomal dominant), associated with early onset AD (<65 yr)
  - 3 major genes, responsible for 5-10% of early onset AD cases, for autosomal dominant AD have been identified:
  - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
  - the ε4 polymorphism of APOE is a susceptibility genotype (ε2 is protective)
  - note: APOE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
- pathology (not necessarily specific for AD)
  - gross pathology
  - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  - microscopic pathology
  - senile β-amyloid plaques (extracellular deposits of amyloid in the grey matter of the brain)
  - loss of synapses
  - neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated tau protein)
  - loss of cholinergic neurons in the nucleus basalis of Meynert that project diffusely throughout the cortex
  - biochemical pathology
  - 50-90% reduction in action of choline acetyltransferase

Down syndrome (trisomy 21) predisposes to early onset of AD (i.e. age 40) due to three copies of the amyloid precursor protein on chromosome 21

Epidemiology

- 1/12 of population 65-75 yr
- up to 1/3 population >85 yr
- very rare <65 yr
- accounts for 60-90% of all dementias (depending on setting and diagnostic criteria)

Risk Factors

- age is the greatest risk factor
- genetic susceptibility polymorphism: APOE ε4 increases risk and decreases age of onset
- other factors include: TBI, FHx, Down syndrome, low education, and vascular risk factors (e.g. smoking, HTN, hypercholesterolemia, DM)

Clinical Features
- cognitive impairment
  - memory impairment for newly acquired information (early)
  - deficits in language, abstract reasoning, and executive function
- behavioural and psychiatric manifestations (80% of those with major NCD)
  - mild NCD: major depressive disorder and/or apathy
  - major NCD: psychosis, irritability, agitation, combativeness, and wandering
- motor manifestations (late)
  - gait disturbance, dysphagia, incontinence, myoclonus, and seizures

Investigations
- perform investigations to rule out other potentially reversible causes of dementia
- EEG: usually normal in mild-moderate stages, slow waves in moderate-advanced stages. May observe generalized slowing (nonspecific)
- MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
- SPECT: hypoperfusion in temporal and parietal lobes
- PET imaging using Pittsburgh compound B (PIB) as a tracer enables imaging of β-amyloid plaque in neuronal tissue
  - FDG-PET can be used to identify regional patterns of cortical hypometabolism and can be helpful to distinguish AD from other causes of dementia (e.g. FTD, DLB)
- LP: β-amyloid protein can be measured in CSF
- Note: common investigations in a clinical setting include ruling out reversible causes with bloodwork, CSF studies, and MRI brain ± EEG. The remainder of the tests are less frequently done or done so in a research setting

Treatment
- **acetylcholinesterase inhibitors** (donepezil, rivastigmine, galantamine) slow the decline in cognitive function
  - do not prolong life expectancy but reduce morbidity
  - relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers, or risk factors for ulcers and/or GI bleeding
  - galantamine contraindication: hepatic/renal impairment
- **NMDA-receptor antagonist** (memantine) that has some benefits in moderate-to-severe AD (i.e. MMSE <17)
- **combination therapy** (acetylcholinesterase inhibitor + NMDA antagonist) is most effective in reducing morbidity
- behavioural symptom management
  1. pharmacologic
     - low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
     - trazodone for sleep disturbance
     - antidepressants (SSRIs)
  2. non-pharmacologic
     - redirection
     - explore inciting factors for behaviour and modify behaviour of patient or caregiver
     - family support and daycare facilities

Prognosis
- mean duration of survival after diagnosis is approximately 10 yr, reflecting the advanced age of the majority of individuals rather than the course of the disease
- death commonly results from aspiration

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment
NEJM 2005;352:2379-88
Purpose: To investigate the efficacy of vitamin E or donepezil in slowing the progression of AD in patients with mild cognitive impairment.
Methods: Patients with the amnestic subtype of mild cognitive impairment were randomly assigned to receive vitamin E (2000 IU daily), donepezil (10 mg daily), or placebo for 3 yr.
Results: Donepezil, but not vitamin E, reduced the likelihood of progression to AD during the first 12 mo (P=0.04), but neither donepezil nor vitamin E significantly reduced the likelihood of progression to AD after 3 yr.
Conclusion: Although donepezil reduced the rate of progression to AD during the first 12 mo, it had no significant effect after 3 yr.

See Landmark Neurology Trial table for more information on the CATIE-AD trial. The trial examined the effects of time and treatment on neuropsychological functioning during the Clinical Antipsychotic Trials of the Intervention Effectiveness-Alzheimer's Disease study.

Major or Mild Neurocognitive Dementia with Lewy Bodies (formerly Dementia with Lewy Bodies)

Definition
- progressive cognitive impairment; early changes in attention, executive, and visuospatial function, recurrent complex visual hallucinations

Clinical Features
- core diagnostic features (probable DLB must have ≥2 core features, possible DLB must have ≥1 core feature):
  - fluctuating cognition with pronounced variations in attention and alertness
  - recurrent visual hallucinations, that are well formed and detailed
  - ≥1 features of parkinsonism (bradykinesia, rest tremor, or rigidity) with onset subsequent to development of cognitive decline
  - REM sleep behaviour disorder
- suggestive/supportive features
  - severe sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms)
  - repeated falls, syncope, or transient episodes of unexplained loss of consciousness
  - auditory or other non-visual hallucinations, systematic delusions, and depression

Etiology and Pathogenesis
- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
- mixed DLB and AD pathology is common

Investigations
- indicative
  - SPECT/PET: low striatal dopamine transporter uptake
- supportive
  - CT/MRI: relative preservation of medial temporal structures
  - SPECT/PET: generalized low uptake with occipital atrophy
  - 123-I-metaiodobenzylguanidine myocardial scintigraphy: low uptake
  - EEG: prominent slow wave activity with temporal lobe transient sharp waves

Epidemiology
- 0.1-5% of the general elderly population
- Lewy bodies are present in 20-35% of all dementia cases (more common in males)

Treatment
- only symptomatic treatments available
- cognitive symptoms: acetylcholinesterase inhibitors (e.g. donepezil and rivastigmine)
- REM sleep behaviour disorder: melatonin, clonazepam (use with caution in patients with cognitive impairment and gait disorders)

Prognosis
- average duration of survival 5-7 yr

Major or Mild Frontotemporal Neurocognitive Dementia (formerly Frontotemporal Dementia)

Definition
- group of disorders caused by progressive frontal or temporal lobes atrophy
  - deficits in executive function (e.g. poor mental flexibility, abstract reasoning, response inhibition, planning/organization, increased distractibility) with relative sparing of learning, memory, and perceptual-motor function
- "probable" is distinguished from "possible" frontotemporal NCD by:
  - Family history or genetic testing: evidence of causative frontotemporal NCD genetic mutation
  - CT/MRI: evidence of disproportionate frontal and/or anterior temporal atrophy
  - SPECT/PET: evidence of frontal and/or anterior temporal hypoperfusion or hypometabolism

Behavioural Variant FTD
- most common variant
- typically early symptom presentation (i.e. within the first 3 yr)
- at least 3/5 of the following symptoms must be present and persistent/recurrent:
  - behavioural disinhibition (socially inappropriate behaviour, impulsive, careless)
  - apathy or inertia (decreased initiation or continuation of behaviour, requiring cues/prompts, less likely to initiate or sustain conversations)
  - loss of sympathy or empathy (diminished response to others' needs/feelings, social interest)
  - preservative, stereotyped, or compulsive/ritualistic behaviour
  - hyperorality and dietary changes (binge eating, increased consumption of EtOH/cigarettes or inedible objects)

Primary Progressive Aphasia (PPA)
- prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension
- three subtypes
  - nonfluent/agrammatic variant PPA (NFAV-PPA) or progressive nonfluent aphasia (PNFA): non-fluent, laboured articulation/speech, anomia, preserved single word comprehension, word-finding deficit, impaired repetition
  - semantic variant PPA (SV-PPA) or semantic dementia (SD): fluent, normal rate, anomia, impaired single word comprehension, intact repetition, use words of generalization ("thing") or supraordinate categories ("animal" for "dog")
  - logopenic progressive aphasia (LPA): naming difficulty and impaired repetition

FTD Movement Disorders
- corticobasal degeneration (CBD) (see *Parkinson's Disease, N33*)
- progressive supranuclear palsy (PSP) (see *Parkinson's Disease, N33*)

Etiology and Pathogenesis
- genetic/familial component (40% have family history of early onset NCD)
- genetic variants: MAPT gene (tau), PGRN gene (progranulin), VCP gene, TARDBP gene (TDP-43), CHMP2D gene, C9ORF72 gene (associated with FTD-ALS)
- gross changes: frontal and anterior temporal lobe atrophy, cortical thinning, possible ventricular enlargement

- histological changes: gliosis, swollen neurons, microvacuolation, inclusion bodies in neurons/glia (Tau or TDP-43)

Epidemiology
- 4th most common cause of dementia (5% of all dementia cases)
- common cause of early-onset NCD in individuals <65 yr

Prognosis
- median survival being 6-11 yr after symptoms onset and 3-4 yr after diagnosis
- survival is shorter and decline is faster than in typical AD

Major or Mild Vascular Neurocognitive Dementia

Definition
- CVD as the dominant if not exclusive pathology that accounts for the cognitive deficits
- vascular etiology suggested by one of the following:
  - onset of cognitive deficits is temporally related to one or more cerebrovascular events
  - for mild vascular NCD: history of a single stroke or extensive white matter disease is sufficient
  - for major vascular NCD: history of two or more strokes, a strategically placed stroke, or a combination
  - evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function
- neuroimaging evidence of CVD:
  - one or more large vessel infarct or hemorrhage
  - a strategically placed single infarct or hemorrhage (e.g. angular gyrus, thalamus, basal forebrain)
  - two or more lacunar infarcts outside the brainstem
  - extensive and confluent white matter lesions
- associated features supporting diagnosis: personality and mood changes, abulia, depression, emotional lability, and psychomotor slowing

Etiology and Pathogenesis
- risk factors: same as CVD (e.g. HTN, DM, smoking, obesity, high cholesterol levels, high homocysteine levels, other risk factors for atherosclerosis, atrial fibrillation, and conditions increasing risk of cerebral emboli)
- major or mild vascular NCD with gradual onset and slow progression is generally due to small vessel disease leading to lesions in white matter, basal ganglia, and/or thalamus
- cognitive deficits can be attributed to disruption of cortical-subcortical circuits

Epidemiology
- second most common cause of NCD
- prevalence estimates for vascular dementia/NCD range from 0.2-13% (by age 70), 16% (ages ≥80) to 44.6% (ages ≥90)
- higher prevalence in African Americans
- prevalence higher in males than in females

Creutzfeldt-Jakob Disease

Definition
- rare degenerative, fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
  - rapidly progressive and common features include cognitive impairment, myoclonus, ataxia, akinetic mutism, weakness, visual changes, etc.
- most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)

Prion proteins have a normal form and an infectious form, which results from conversion of the protein from α-helix (normal) to β-pleated sheet (abnormal); these abnormally folded proteins aggregate leading to neuronal loss

Investigations
- CSF analysis, MRI brain (cortical (i.e. cortical ribbon sign) and/or subcortical (i.e. hockey stick sign) FLAIR changes), EEG (periodic complexes), real-time quaking-induced conversion
- definitive diagnosis is by brain biopsy

Treatment
- symptomatic management of seizures and movement disorders, and neuropsychiatric symptoms but there is no known cure for CJD

Aphasia

Definition

- an acquired disturbance of language characterized by errors in language production, writing, comprehension, or reading

Relevant Neuroanatomy

- Broca's area (posterior inferior frontal lobe) is involved in language production (expressive)
- Wernicke's area (posterior superior temporal lobe) is involved in comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke's area for reading comprehension
- arcuate fasciculus association bundle connects Wernicke's and Broca's areas

Assessment of Language

- assessment of context
  - handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
- assessment of aphasia
  - spontaneous speech (fluency, paraphasias, repetition, naming, writing, neologism, comprehension – auditory and reading)

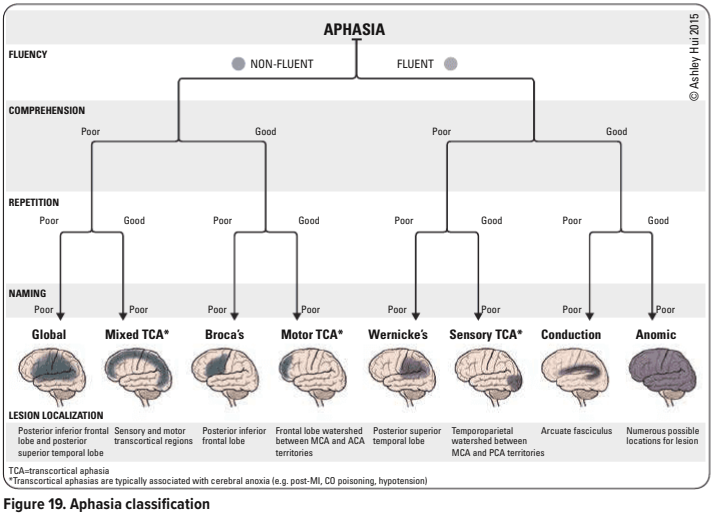


Figure 19. Aphasia classification

>99% of right-handed people have left hemisphere language representation
70% of left-handed people have left hemisphere language representation, 15% have right hemisphere representation, and 15% have bilateral representation

Types of Paraphasias
Semantic (e.g. "chair" for "table")
Phonemic (e.g. "clable" for "table")

Aphasia localizes the lesion to the dominant cerebral hemisphere

Apraxia

Definition

- inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension, or inattention

Clinicopathological Correlations

Table 15. Apraxia

	Description	Tests	Hemispheres
Ideomotor	Inability to perform skilled learned motor sequences	Blowing out a match, combing one's hair	Left
Ideational	Inability to sequence actions	Preparing and mailing an envelope	Right and left
Constructional*	Inability to draw or construct	Copying a figure	Right and left
Dressing*	Inability to dress	Dressing	Right

*Refers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks.

Agnosia

Definition

- inability to recognize the significance of sensory stimuli in the presence of intact sensation and naming

Clinicopathological Correlations

Table 16. Agnosias

	Description	Lesion
Apperceptive Visual Agnosia	No visual defect but inability to recognize objects	Bilateral temporo-occipital cortex
Associative Visual Agnosia	Inability to name an object presented visually, 2º to disconnect between visual cortex and language areas Visual perception is intact as demonstrated by visual matching	Bilateral inferior temporo-occipital junction
Prosopagnosia	Inability to recognize familiar faces in the presence of intact visual perception and intact auditory recognition	Bilateral temporo-occipital areas or right inferior temporo-occipital region
Colour Agnosia	Inability to perceive colour	Bilateral inferior temporo-occipital lesions
Impaired Stereognosis	Inability to identify objects by touch	Anterior parietal lobe in the hemisphere opposite to the affected hand
Finger Agnosia	Inability to recognize, name, and point to individual fingers	Dominant hemisphere parietal-occipital lesions

Lesions of the dominant parietal lobe are characterized by Gerstmann's syndrome: acalculia, agraphia, finger agnosia, and left-right disorientation

Lesions of the non-dominant parietal lobe are characterized by neglect, anosognosia, and asomatognosia

Cortical sensory loss (graphesthesia, astereognosis, impaired 2-point discrimination, and extinction) can be seen with left or right parietal lesions

Mild Traumatic Brain Injury

Definition

- mild TBI = concussion
- trauma-induced transient alteration in mental status that may involve loss of consciousness
- hallmark symptoms: confusion and amnesia, which may occur within minutes
- loss of consciousness (if present) less than 30 min, initial GCS between 13-15, post-traumatic amnesia <24 h

Extent of retrograde amnesia correlates with severity of injury
Regained from most distant to recent memories

Epidemiology

- 75% of TBIs are estimated to be mild; the remainder are moderate or severe (see Neurosurgery, *Brain Injury*, NS37and Emergency Medicine, ER9)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features

- impairments following mild TBI
  - physical: headache, sleep disturbance (hypersomnia or insomnia), nausea, vomiting, and blurred vision, photophobia, phonophobia, dizziness
  - cognitive dysfunction: attentional impairment, slowed reaction time, drowsiness, amnesia, confusion, executive function impairment
  - emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
- associated conditions: brain contusion, diffuse axonal injury, C-spine injury

Investigations

- neurological exam to identify focal neurologic deficits
- neurocognitive assessment
  - simple orientation questions are inadequate to detect cognitive changes
  - initial assessment of severity is determined by GCS
    - mild: 13-15, moderate: 9-12, severe: 3-8
  - sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool
- neuroimaging
  - x-ray skull: not indicated for routine evaluation of mild TBI
  - CT head as indicated by Canadian CT Head Rules
  - MRI not indicated in initial evaluation; consider if continued or worsening symptoms despite normal CT

Treatment

- minimum hourly clinical observations until at least 4 h post injury
- hospitalization if CT is abnormal, or if CT is normal but symptoms not improving at 4-6 h post injury
- early rehabilitation to maximize outcomes
  - occupational therapy (OT), physical therapy (PT), speech-language pathology (SLP), vestibular therapy, driving, therapeutic recreation, sleep hygiene
- pharmacological management of headaches, pain, depression
- cognitive behavioural therapy, relaxation therapy
- follow Return to Play guidelines (www.thinkfirst.ca)

Prognosis

- most recover from mild TBI with minimal treatment, but some experience long-term consequences
- patients with a previous concussion are at increased risk of subsequent concussions and cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
- sequelae include:
  - post-concussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within wk to mo)
  - post-traumatic headaches: begin within 7 d of injury
  - post-traumatic epilepsy: approximately 2% risk post-mild TBI; prophylactic anticonvulsants are not effective
  - post-traumatic vertigo

Neuro-Oncology

Paraneoplastic Syndromes

- see Endocrinology, E56

Tumours of the Nervous System

- see Neurosurgery, NS12

Movement Disorders

Basal Ganglia

- formed by the caudate, putamen, globus pallidus, subthalamic nucleus, and substantia nigra
- input from cerebral cortex, output to thalamus
- direct pathway: promotes movement, indirect pathway: inhibits movement

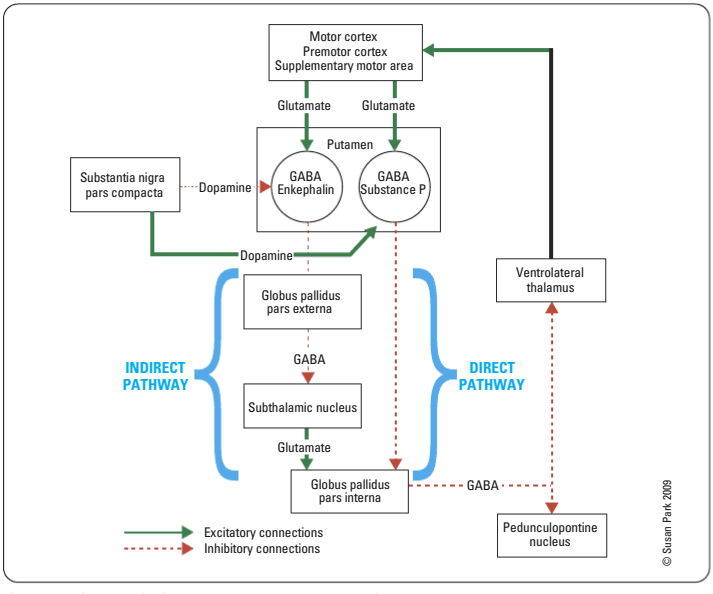


Figure 20. Direct and indirect pathways of the basal ganglia

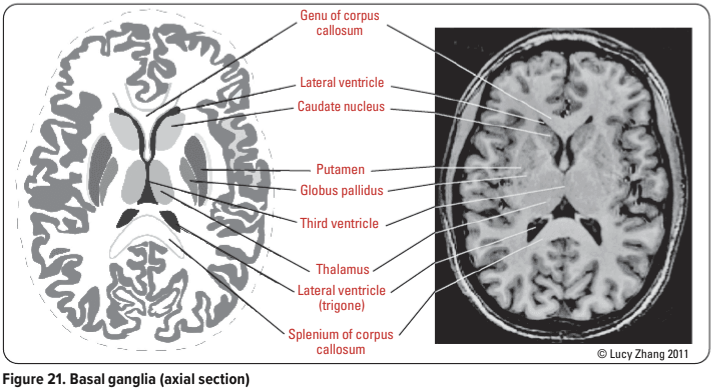


Figure 21. Basal ganglia (axial section)

Signs and Symptoms of Movement Disorders

Table 17. Movement Disorder Definitions

Akathisia	Subjective generalized restlessness relieved by voluntary stereotypic movements (e.g. squirming)
Asterixis	Transient loss of muscle tone (negative myoclonus)
Athetosis	Slow writhing movements, especially distally
Ballism	Large-amplitude, involuntary, flinging movements that are most commonly unilateral (hemiballism)
Bradykinesia	Slow, small amplitude movements
Chorea	Brief, unpredictable, irregular movements, flowing from one body part to another; can appear purposeful in milder forms
Dysdiadochokinesia	Inability to smoothly perform rapidly alternating movements
Dyskinesia	Any involuntary movement, but the term is often used to describe the stereotypical movements that come with long-term neuroleptic use (tardive dyskinesia) or levodopa use (levodopa induced dyskinesia)
Dystonia	Co-contraction of agonist and antagonist muscles causing sustained twisting movements which can be tonic (dystonic postures) or phasic (dystonic movements)
Freezing	Episodes of halted motor action, especially during repetitive actions (e.g. walking)
Myoclonus	Brief muscle group contraction that is either focal, segmental, or generalized
Myokymia	Spontaneous, fine, fascicular contraction of muscle
Stereotypies	Predictable, repetitive, involuntary movements that do not appear to have any purpose (commonly associated with intellectual disability or autism)
Tachykinesia	Acceleration of movements e.g. accelerated walking (festination)
Tics	Stereotyped, nonrhythmic, and brief repetitive actions due to inner urge Can be phonic (vocal) or motor and can be suppressed
Tremor	Rhythmic and involuntary antagonistic muscle alternating/oscillating contractions

In some cases, dystonias may occur only during voluntary movements and sometimes only during specific activities, such as writing, chewing, or speaking (task-specific dystonia)

Hemiballism is most often due to a vascular lesion

Myoclonus can be stimulus-sensitive (induced by sudden noise, movement, light, visual threat, or pinprick)

Tremor

Table 18. Approach to Tremors

	Resting Tremor	Action-Postural Tremor	Action-Intention Tremor
Affected Body Part	Upper limb >jaw>lower limb>head	Upper limb>head>lower limb>tongue	Upper limb>voice>Lower limb
Characteristics	3-6 Hz pill-rolling	6-12 Hz fine tremor	<5 Hz coarse tremor
Worse with Associated Sx	Rest while concentrating "TRAP"	Sustained posture (outstretched arms) ± Autosomal dominant FHx	Finger to nose Cerebellar findings
DDx	PD, parkinsonism, Wilson's disease, mercury poisoning, severe essential tremor	Physiologic, essential tremor, hyperthyroidism, hyperglycemia, heavy metal poisoning, CO poisoning, drug toxicity, sedative/EtOH withdrawal	Cerebellar disorders, Wilson's disease, MS, ASMs, EtOH, sedatives
Treatment	Levodopa/carbidopa (Sinemet®), DBS	Propranolol, primidone, topiramate, and other ASMs, surgery (thalamotomy, DBS)	Treat underlying cause

In a young patient (<45 yr) must do TSH (thyroid disease), ceruloplasmin (Wilson's disease), and CT/MRI (cerebellar disorder) as indicated by type of tremor

Most of the time, essential tremor does not need treatment

Alcohol

Dampens essential tremor

Potentiates intention tremor during abstinence (delirium tremens)

Does not improve resting tremor of PD

Chorea

- HD, HD-like syndromes, neuroacanthocytosis, SLE, antiphospholipid antibodies (APLA) syndrome, Wilson's disease, CVD, tardive dyskinesia, senile chorea, Sydenham's chorea, pregnancy chorea (chorea gravidarum), levodopa-induced dyskinesia

Most common cause of chorea is drug therapy for PD (levodopa-induced dyskinesia)

Dystonia

- **primary dystonia**: familial, sporadic (torticollis, blepharospasm, writer's cramp)
- **dystonia-plus syndromes**: dopa-responsive dystonia, myoclonus-dystonia
- **secondary dystonia**: stroke, CNS tumour, demyelination, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
- **heredodegenerative dystonias**: Parkinsonian disorders, Wilson's disease, HD

Myoclonus

- **physiologic myoclonus**: hiccups, nocturnal myoclonus
- **essential myoclonus**: myoclonus-dystonia with minimal or no occurrence of dystonia
- **epileptic myoclonus**
- **symptomatic myoclonus**
- **degenerative disorders**: Wilson's disease, HD, corticobasal degeneration
- **infectious disorders**: CJD, viral encephalitis, AIDS-dementia complex
- **metabolic disorders**: drug intoxication/withdrawal, hypoglycemia, hyponatremia, hyperglycemic hyperosmolar syndrome, hepatic encephalopathy, uremia, hypoxia
- **focal brain damage**: head injury, stroke, mass

Palatal tremor can result from lesion to the dentato-rubro-olivary tract

Parkinson's Disease

Etiology
- sporadic: combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- familial (10%): autosomal dominant α-synuclein or LRRK2 mutations, autosomal recessive parkin, PINK1, or DJ-1 mutation (juvenile onset)
- MPTP (neurotoxin)

Epidemiology
- prevalence of 0.3% in industrialized countries, but rises with increased age
- second most common neurodegenerative disorder, after AD
- mean age of onset is 60 yr

Associated Factors
- risk: family history, male, head injury, rural living, exposure to certain neurotoxins
- protective: coffee drinking, smoking, estrogen replacement in post-menopausal women

Pathophysiology
- α-synucleinopathy: α-synuclein accumulates intracellularly as Lewy bodies and Lewy neurites leading to neuronal loss
- pathological progression of α-synuclein explains onset clinical features: dorsal motor nucleus of the vagus (medulla) and olfactory bulbs (constipation, anosmia) pons (REM sleep behaviour disorder) midbrain, substantia nigra pars compacta, and cortex (cognitive impairment, hallucinations)
- motor symptoms emerge when 70% loss of dopaminergic neurons in substantia nigra pars compacta → decreased dopamine in striatum → 1. disinhibition of the indirect pathway, and 2. decreased activation of the direct pathway → increased inhibition of cortical motor areas

Clinical Features
- diagnosis is based on clinical features:
  1. **bradykinesia**
     - bradykinesia: slow, small amplitude decrementing movements, fatigue from rapid alternating movements, difficulty initiating movement
  2. **resting tremor or rigidity**
     - resting tremor: typically 4-6 Hz "pill-rolling" tremor, especially in hands
     - cogwheel rigidity: increased muscle tone with superimposed tremor
  3. **asymmetric onset of tremor, rigidity, bradykinesia**
  4. **progressive course**
  5. **other signs and symptoms**
     - hypomimia (reduced facial expression), hypophonia, aprosodia (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
     - freezing of gait: occurs with walking triggered by initiating stride or barriers/reaching destinations, lasting seconds
     - postural instability: a late finding that presents as falls
     - cognition: bradyphrenia (slow to think/respond), dementia (late finding)
     - behavioural: decreased spontaneous speech, depression, sleep disturbances, anxiety
     - autonomic: constipation, urinary dysfunction (nocturia, urgency, frequency), sexual dysfunction, orthostatic hypotension, clinostatic HTN
     - sleep: REM sleep behaviour disorder, insomnia, hypersomnolence

Treatment
- **pharmacologic**
  - levodopa/carbidopa (Sinemet®) or levodopa/benserazide (Prolopa®)
  - levodopa is a dopamine precursor, carbidopa/benserazide decrease levodopa peripheral metabolism, decreasing levodopa side effects and increasing its half-life
    - levodopa-related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration ("wearing-off"), random oscillations of on-off symptoms
    - major adverse effect of levodopa: dyskinesia
  - treatment of early PD: levodopa, dopamine agonists, amantadine, MAOI
  - adjuncts: dopamine agonists, MAOI, anticholinergics (especially if prominent tremors), catechol-O-methyltransferase inhibitors
- **surgical** (for patients who respond to levodopa but with debilitating motor fluctuation/dyskinesia)
  - thalamotomy
  - pallidotomy
  - DBS (thalamic, pallidal, subthalamic)
- **psychiatric**
  - SSRIs first line
  - TCAs (beware fall risk, cognitive impairment, and worsening symptoms of PD)

Key Parkinsonian Features

TRAP
Tremor (resting)
Rigidity
Akinesia/bradykinesia
Postural instability

2015 Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD

"Clinically established PD" requires:

Cardinal Parkinsonism Manifestations: Bradykinesia with either resting tremor or rigidity

2 or more supportive criteria (clear and dramatic beneficial response to dopaminergic therapy, levodopa-induced dyskinesia, rest tremor of a limb, and/or olfactory loss/cardiac sympathetic denervation on MIBG scintigraphy)

No absolute exclusion criteria and no red flags (see full diagnostic criteria - Mov Disord 2015;30:1591-601)

Consider an Alternative Diagnosis if Atypical Parkinsonism

Poor response to levodopa

Abrupt onset of symptoms

Rapid progression

Early falls

Early autonomic dysfunction

Symmetric symptoms at onset

Early age of onset (<50 yr)

Early cognitive impairment

FHx of psychiatric disorders and/or dementia

Recent diagnosis of psychiatric disease

History of encephalitis

Unusual toxin exposure

Extensive travel history

Other Parkinsonian Disorders

- NCD with Lewy bodies: see *Behavioural Neurology, N21*
- progressive supranuclear palsy (PSP): tauopathy; limited vertical gaze (downgaze more specific, can be overcome by the oculocephalic reflex), early postural instability (frequent falls, wide-based unsteady gait), axial rigidity, akinesia, dysarthria, dysphagia; little or no response to levodopa
- corticobasal syndrome: tauopathy; unilateral parkinsonism, dystonia/myoclonus, and apraxia ± "alien limbs" phenomenon; ± progressive non-fluent aphasia; unlikely to respond to levodopa
- MSA: synucleinopathy; cerebellar predominant (MSA-C) or parkinsonism predominant (MSA-P); early autonomic dysfunction (urinary incontinence or orthostatic hypotension)
- vascular parkinsonism: multi-infarct presentation with gait instability and lower body parkinsonism; stepwise decline over time; less likely associated with tremor

Huntington's Disease

Etiology and Pathogenesis

- genetics: autosomal dominant cytosine-adenine-guanine (CAG) repeats in HTT gene on chromosome 4, which leads to accumulation of defective protein in neurons; autosomal dominant inheritance; genetic anticipation where CAG repeats increase in size with subsequent generations
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway, and decreased activity of the indirect pathway

Epidemiology

- North American prevalence 4-8 in 100000
- mean age of onset 35-44 yr, but varies with degree of anticipation from 5-70 yr

Clinical Features

- typical progression: insidious onset with clumsiness, fidgetiness, and irritability, progressing over 15 yr to major NCD, psychosis, and chorea
  - major NCD: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudo-purposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence
- Juvenile-onset HD (Westphal variant) characterized by parkinsonism, dystonia, rigidity, seizures

Investigations

- MRI
  - enlarged ventricles, atrophy of cerebral cortex, and caudate nucleus
- genetic testing
  - CAG trinucleotide repeats in HTT on chromosome 4p16.3
  - CAG repeat sizes that result in meiotic instability (27-35 repeats), reduced disease penetrance (36-39 repeats), and full disease penetrance (≥40 repeats)

Treatment

- no disease-modifying treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: tetrabenazine, amantadine, and neuroleptics
- dystonia: botulinum toxin (for focal dystonia)

Wilson's Disease

- see Gastroenterology, G37

Dystonia

Epidemiology

- 3rd most common movement disorder after PD and essential tremor

Clinical Features

- abnormal posturing, sustained or intermittent twitching movements caused by co-contraction of agonist and antagonist muscles
- symptoms exacerbated by fatigue, stress, and emotions; relieved by sleep or specific tactile/proprioceptive stimuli (sensory tricks, e.g. placing hand on face for cervical dystonia)
- more likely to be progressive and generalized if younger onset or leg dystonia

Dopamine Agonist Therapy in Early Parkinson's Disease
Cochrane DB Syst Rev 2009;2:CD006564
Study: Meta-analysis of trials of dopamine agonists in early PD.
Results: Twenty-nine trials were included (n=5247). Dopamine agonists were found to have decreased motor side effects (dyskinesia (OR 0.51), dystonia (OR 0.64), motor **fluctuations** (OR 0.75), but provided poorer symptom control compared to levodopa. Also, other side effects were increased (constipation (OR 1.59), hallucinations (OR 1.69), dizziness (OR 1.45)).
Conclusion: Dopamine agonists have fewer motor side effects than levodopa, but provide worse symptom control and increased rate of other side effects.

Treatment
- local medical: botulinum toxin
- systemic medical: anticholinergics (trihexyphenidyl, benztropine), muscle relaxants (baclofen), benzodiazepines, dopamine depletors (tetrabenazine), dopamine for dopa-responsive dystonia
- surgical: DBS or denervation of affected muscle

Tic Disorders

Definition
- sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
- common criteria
  - onset <18 yr
  - tics may wax and wane in frequency but have persisted for an extended period of time
  - disturbance is not attributable to the physiological effects of a substance or another medical condition

Classification
- **Tourette's syndrome**: multiple motor and ≥1 vocal tics that have persisted for >1 yr since onset
- **persistent (chronic) motor or vocal tic disorder**: single or multiple motor or vocal tics (but not both motor and vocal) that have persisted for >1 yr since onset
- **provisional tic disorder**: single or multiple motor and/or vocal tics present for <1 yr since first tic onset
- **other specified or unspecified tic disorder**: symptoms characteristic of a tic disorder but do not meet full criteria
- **secondary tic disorders**: encephalitis, CJD, Sydenham's chorea, head trauma, drugs (stimulants, levodopa), intellectual disability syndromes
- **neurodegenerative diseases**: neuroacanthocytosis, HD (see *Huntington's Disease, N34*)

Tic Types
- simple tics: short duration (msec)
- complex tics: longer (s), more purposeful and often include a combination of simple tics
- motor tics
  - simple: blinking, head jerking, shoulder shrugging, extension of the extremities
  - dystonic: bruxism (grinding teeth), abdominal tension, sustained mouth opening
  - complex: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- vocal tics
  - simple: blowing, coughing, grunting, throat clearing
  - complex: coprolalia (shout obscenities), echolalia (repeat others' phrases), palilalia (repeat own phrases)

Treatment
- indicated if quality of life affected
- mild tics: education, counselling, supportive care, Comprehensive Behavioural Intervention for Tics
- debilitating tics: α-2 adrenergic agonists (guanfacine, clonidine), antipsychotics (e.g. haloperidol, pimozide), botulinum toxin, topiramate, DBS

Tourette's Syndrome

DSM-V Definition
1. presence of both multiple motor and one or more vocal tics at some point during the illness, although not necessarily concurrently
2. tics may wax and wane in frequency but have persisted >1 yr since first tic onset (with no tic-free periods >3 mo)
3. onset <18 yr
4. not due to effect of a substance or another medical condition

Epidemiology
- estimated prevalence among adolescents 3-8 in 1000 school-age children, M:F=2-4:1

Signs and Symptoms
- tics: wide variety that wax and wane in type and severity (see *Tic Disorders – Tic Types*)
  - can be associated with the presence of premonitory feelings or sensations that are relieved by carrying out the tic
  - can be voluntarily suppressed for some time
  - can be worsened by anxiety, excitement, and exhaustion; improved by calm, focused activities
- psychiatric: compulsive behaviour (associated with obsessive-compulsive disorder (OCD) and Attention-Deficit/Hyperactivity Disorder (ADHD)), hyperactive behaviour, "rages," sleep-wake disturbances, or learning disabilities

Treatment
- mild tics: (see *Tic Disorders –Treatment, N35*)
- debilitating tics: (see *Tic Disorders –Treatment, N35*)

Prognosis
- typically begins between ages 4-6
- peak severity occurs between ages 10-12, with a decline in severity during adolescence (50% are tic-free by age 18)
- tic symptoms, however, can manifest similarly in all age groups and across the lifespan

Cerebellar Disorders

Cerebellar Signs and Symptoms
- symptoms ipsilateral to side of lesion
- limb ataxia (if involvement of lateral zone of cerebellar hemisphere)
  - dysmetria (uncoordinated movements, assessed with finger-to-nose and heel-to-shin tests)
  - intention tremor (tremor that worsens at end of goal-directed movement)
  - dysdiadochokinesia (inability to perform rapid alternating movements)
  - hypotonia causing pendular reflexes
  - Holmes rebound phenomenon (exaggerated movement after resistance is removed)
- truncal ataxia (if involvement of cerebellar vermis)
  - wide-based gait
  - inability to perform heel-to-toe (tandem) gait
  - truncal titubation
- nystagmus (often gaze-evoked), hypermetric or hypometric saccades, impaired smooth pursuit
- scanning speech (explosive speech with noticeable pauses and accentuated syllables)

Wernicke-Korsakoff Syndrome

- acute (Wernicke's encephalopathy) and chronic (Korsakoff's psychosis) disorders caused by thiamine (vitamin B1) deficiency, see Psychiatry, PS29
- etiology: alcohol use disorder, gastrointestinal disorders especially malabsorption, surgeries (e.g. gastric bypass), malnutrition, acquired immune deficiency syndrome, hemodialysis, malignancies
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy

Cerebellar Ataxias

Congenital Ataxias
- early onset non-progressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

Hereditary Ataxias
- autosomal recessive: Friedrich's ataxia, ataxia with oculomotor apraxia, ataxia telangiectasia, ataxia with vitamin E deficiency
  - Friedrich's ataxia: prevalence 2 in 100000; typical onset between 8-15 yr
  - signs: gait and limb ataxia, weakness, areflexia, extensor plantar response, impaired proprioception and vibration, dysarthria, nystagmus
  - death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- autosomal dominant: most commonly spinocerebellar ataxias (SCAs); 30+ types, most commonly due to CAG repeats
  - signs: ataxia and dysarthria, chorea, polyneuropathy, pyramidal, and/or extrapyramidal features, dementia

Acquired Ataxias
- neurodegeneration: multiple system atrophy, SCAs
- systemic: alcohol, celiac sprue, hypothyroidism, Wilson's, thiamine deficiency, vitamin E deficiency
- toxins: CO, heavy metals, lithium, anticonvulsants, solvents
- vascular: infarct, bleed, basilar migraine
- autoimmune: MS, Miller-Fisher variant of GBS
- primary or secondary neoplasm

Vertigo

- see Otolaryngology, OT12

Motor Neuron Disease

Amyotrophic Lateral Sclerosis

Definition
- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal
- also known as Lou Gehrig's disease

Etiology
- idiopathic (most common), genetic (5-10% familial, most commonly C9orf72 mutation, other mutations include: SOD1, TARDBP)

Pathology
- disorder of lower motor neurons of the spinal cord and cranial nerve motor nuclei, and upper motor neurons of the corticospinal tract

Epidemiology
- 5 in 100000; incidence increases with age

Clinical Features
- UMN symptoms
  - poor dexterity
  - spasticity (spastic gait)
  - hyperreflexia
  - bulbar findings: dysarthria (spastic; strained vocal quality with slow speech), dysphagia, pseudobulbar affect, laryngospasm
- LMN symptoms
  - weakness (of hands, arms, tongue, pharyngeal muscles, lips, eyelids, masseters and pterygoids, diaphragm)
  - muscle atrophy
  - fasciculations
  - muscle cramps
  - bulbar findings: dysarthria (flaccid; slurred and may have a nasal quality) and dysphagia
- cognitive and behavioural dysfunction, FTD (~15%)
- sensory symptoms uncommon (20-30%)

Investigations
- EMG: to assess active and chronic denervation and reinnervation, fasciculations
- NCS: to rule out peripheral neuropathy (e.g. multifocal motor neuropathy with conduction block)
- MRI brain and spine: to exclude alternative diagnoses and evaluate LMN, UMN, and bulbar findings
- genetic testing: to look for pathogenic variants in patients with familial ALS

Treatment
- riluzole (been shown to slow disease progression and prolong survival)
- edaravone (been shown to slow functional decline by 33% in early-stage ALS)
- sodium phenylbutyrate-taurursodiol (PB-TURSO; been shown to slow clinical deterioration)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine (Zanaflex®), regular exercise, and physical therapy
  - sialorrhea: TCA (e.g. amitriptyline), sublingual atropine drops, parotid, and/or submandibular Botox® (rare)
  - pseudobulbar affect: dextromethorphan and quinidine, TCA, SSRI
- non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (e.g. percutaneous endoscopic gastrostomy tube), rehabilitation (PT, OT, SLP), and psychosocial support

Prognosis
- median survival is 3 yr; death is typically due to respiratory failure

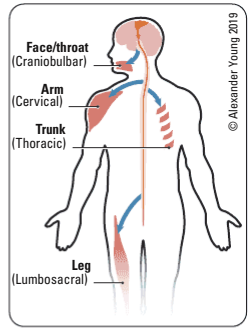


Figure 22. Regions affected by ALS
Adapted from: https://www.mda.org/disease/amyotrophic-lateral-sclerosis/signs-and-symptoms and labels: ALS and Other Motor Neuron Diseases (2017) Lecture by Dr. Aaron Izenberg

Safety and Efficacy of Edaravone in Well Defined Patients with Amyotrophic Lateral Sclerosis: A Randomised, Double-Blind, Placebo-Controlled Trial
Lancet Neurol 2017;16:505-12
Purpose: To assess the safety and efficacy of edaravone in patients with early-stage ALS.
Methods: 137 early-stage ALS patients meeting stringent inclusion criteria were randomly assigned to receive 60 mg IV edaravone or IV saline placebo for 6 cycles (4 wk/cycle with 2 wk on, 2 wk off) for a total treatment duration of 24 wk.
Primary Outcome: Difference in the Revised ALS Functional Rating Scale (ALSFRS-R) score from baseline to 24 wk.
Results: The ALSFRS-R score change was -5.01 (SE 0.64) and -7.50 (0.66) in the edavarone group and placebo, respectively. The between-group least-squares mean difference was 2.49 (SE 0.76, 95% CI 0.99-3.98; P=0.0013), thus favouring edaravone. Adverse events were similar in both groups.
Conclusion: In early-stage ALS patients identified in post-hoc analysis of a previous phase 3 study, edaravone significantly reduced the decline of ALSFRS-R scores.

The only interventions shown to extend survival in ALS are riluzole and use of BiPAP. Edavarone in early ALS can decrease functional decline

Red Flags Inconsistent with ALS
Sensory Sx, predominant pain, bowel or bladder incontinence, extraocular muscle weakness

Denervation on EMG
Fibrillations, positive sharp waves, complex repetitive discharges

Reinnervation on EMG
Increased amplitude and duration of motor units

Other Motor Neuron Diseases

- degenerative
  - **progressive muscular atrophy (progressive bulbar palsy):** only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centres (considered the isolated LMN version of ALS)
  - **primary lateral sclerosis (progressive pseudobulbar palsy):** UMN symptoms, later onset, not fatal, variable disability, 5-10% of patients in ALS centres (considered the isolated UMN version of ALS)
  - **progressive bulbar palsy**: UMN and LMN disorder of cranial muscles, bulbar symptoms
- genetic
  - **spinal muscular atrophy**: pediatric or adult-onset disease with symmetric LMN symptoms (genetic disorder)
  - **spino-bulbar muscular atrophy (Kennedy disease):** speech and swallowing difficulty and limb weakness (X-linked genetic)
- infectious
  - **post-polio syndrome**: muscle weakness usually many years after a poliomyelitis infection
  - **West Nile infection**: residual asymmetric muscle weakness, atrophy

Peripheral Neuropathies

Approach

1. differentiate: motor vs. sensory vs. autonomic vs. mixed
2. pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; CN involvement
3. temporal pattern: acute vs. chronic; relapsing/remitting vs. constant vs. progressive
4. history: PMHx, detailed FHx, exposures (e.g. insects, toxins, sexual, travel), systemic symptoms
5. detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status

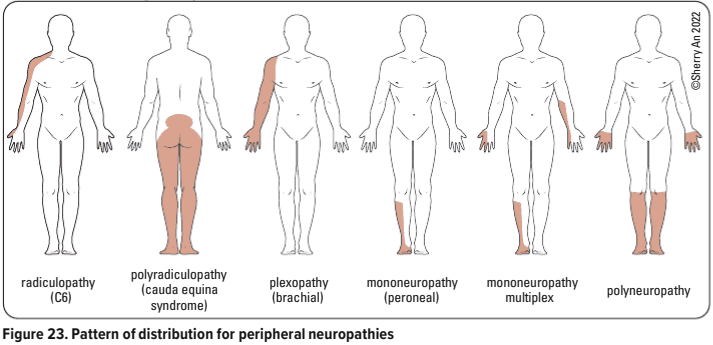


Figure 23. Pattern of distribution for peripheral neuropathies

Classification

- **radiculopathy**: dermatomal sensory deficit and myotomal weakness in distribution of single nerve root (e.g. C7)
  - often due to disc herniation or root compression causing radicular pain
  - little tactile anesthesia, as dermatomes overlap
- **polyradiculopathy**: multiple dermatome sensory deficits and myotomal weakness
  - due to multiple nerve root lesions (e.g. cauda equina syndrome due to lumbosacral roots lesion)
- **plexopathy**: deficit matching distribution of a nerve plexus
  - due to lesion distal to nerve roots but proximal to origin of individual peripheral nerves
  - **brachial plexopathy**
    - upper (C5-C7): LMN Sx of shoulder and upper arm muscles (Erb's palsy)
    - lower (C8-T1): LMN Sx and sensory Sx of forearm and hand (Klumpke's palsy)
    - DDx: trauma, idiopathic neuritis, tumour infiltration, radiation, thoracic outlet syndrome (e.g. cervical rib)
  - **lumbosacral plexopathy** (rare, especially unilateral)
    - DDx: idiopathic neuritis, infarction (e.g. DM), compression
- **mononeuropathy**: single nerve deficit
  - **carpal tunnel syndrome (most common):** compression of median nerve at wrist
    - symptoms: wrist pain, paresthesia first 3 and ½ digits, ± radiation to elbow, worse at night
    - signs: Tinel's sign, Phalen's test, thenar muscle wasting, sensory deficit
    - EMG/NCS: slowing at wrist (both motor and sensory)
    - etiology: entrapment, pregnancy, DM, gammopathy, rheumatoid arthritis, thyroid disease
  - **Bell's palsy (most common cranial neuropathy):** see Otolaryngology, OT22

Diabetic Neuropathies

Peripheral neuropathy: pain or loss of sensation in a stocking-glove distribution (hands and feet affected before arms and legs)

Autonomic neuropathy: tachycardia, anhidrosis, orthostatic hypotension, gastroparesis, GERD, bowel and bladder dysfunction, erectile dysfunction

Mononeuropathy multiplex: nerve infarct or compression

Cranial neuropathy: CN III (pupil sparing) > IV > VI

Lumbosacral plexopathy (i.e. diabetic amyotrophy): unilateral leg pain and weakness, unintentional weight loss

DDx of Demyelinating Neuropathy

GBS, CIDP, paraproteinemia, diphtheria, amiodarone, Charcot-Marie-Tooth (including hereditary neuropathy with liability to pressure palsy), storage diseases, pressure palsy predisposition, paraneoplastic

Tinel's Sign

Tap lightly over the median nerve at the wrist; the patient's symptoms of carpal tunnel will be elicited in a positive test

Phalen's Test

Hold both wrists in forced flexion (with the dorsal surfaces of the hands pressed against each other) for 30-60 s; test is positive if symptoms of carpal tunnel are elicited

Axonal neuropathies have decreased amplitude on NCS; demyelinating neuropathies have decreased conduction velocity on NCS

Ototoxic drugs (e.g. aminoglycosides) should not be given to diabetic patients Sensory neuropathy of the feet prevents these patients from adequately compensating for loss of vestibular function

- **entrapment/compression:** ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)

- **mononeuropathy multiplex**: subacute involvement of multiple individual peripheral nerves in asymmetric, non-length-dependent manner; often painful
  - must rule out vasculitis or collagen vascular disease; consider MMN (multifocal motor neuropathy) or MADSAM (multifocal acquired demyelinating sensory and motor neuropathy), multiple compressive neuropathies
- **polyneuropathy**: chronic progressive involvement of multiple peripheral nerves in symmetrical, distal-predominant pattern
  - length-dependent, i.e. longest fibres affected first (stocking-glove distribution)
  - sensorimotor, with progression of dysesthesia earlier and weakness later
  - etiology: DM (most common), renal disease, substances, toxins, genetic, SLE, HIV, leprosy, alcohol, vitamin B12 deficiency
  - **CIDP**
    - chronic relapsing sensorimotor polyneuropathy or polyradiculopathy with increased protein in CSF and demyelination (shown on EMG/NCS)
    - course is fluctuating, in contrast with the acute onset of GBS
    - treatment: first-line is prednisone; alternatives are plasmapheresis, IVIG, and azathioprine

Evaluation of Distal Symmetric Polyneuropathy: Role of Laboratory and Genetic Testing
Neurology 2009;72:185-192
Screening Lab Tests: Blood glucose, serum vitamin B12 with metabolites, serum protein immunofixation electrophoresis.
Genetic Testing: Indicated for cryptogenic polyneuropathy exhibiting classic hereditary neuropathy phenotype. Screen for CMT1A duplication/deletion and Cx32 mutations.

Table 19. Differential Diagnosis of Symmetric Polyneuropathy

	Etiology	Mechanism	Course	Modalities	Investigations
Vascular*	PAN	Ischemic	Chronic	S/M	See Rheumatology, RH21
	SLE	Ischemic	Chronic	S/M	See Rheumatology, RH11
	RA	Ischemic	Chronic	S/M	See Rheumatology, RH8
Infectious	HIV	Axonal	Chronic	S/A	HIV serology
	Leprosy	Infiltrative	Acute	S/A	Leprosy serology Nerve biopsy
	Lyme	Axonal	Chronic	M	Lyme serology
Immune+	GBS	Demyelination	Acute	M	LP (↑ protein, no ↑ cells) EMG
	CIDP	Demyelination	Chronic	S/M	LP (↑ protein) EMG
Hereditary	HMSN	Axonal/demyelination	Chronic	S/M	Genetic testing
Neoplastic	Paraneoplastic	Axonal/demyelination	Chronic	S/M	Paraneoplastic antibodies
	Myeloma	Axonal/demyelination	Chronic	S/M	SPEP Skeletal bone survey
	Lymphoma	Axonal	Chronic	M	SPEP Bone marrow biopsy
	Monoclonal gammopathy	Axonal/Demyelination	Chronic	S/M	SPEP Bone marrow biopsy
Toxin	EtOH	Axonal	Sub-acute	S/M	GGT, MCV
	Heavy metals (e.g. lead)	Axonal	Sub-acute	S/M	Urine heavy metals
	Medications	Axonal	Sub-acute	S/M	Drug levels
Metabolic	DM	Ischemic/axonal	Chronic	S/A	Fasting glucose, HbA1c, 2 h OGTT
	Hypothyroidism	Axonal	Chronic	S/M	TSH, T3, T4
	Renal failure	Axonal	Chronic	S/A	Electrolytes, Cr, BUN
Nutritional	B_{12}deficiency	Axonal	Sub-acute	S/M	Vitamin B_{12}
Other	Porphyria	Axonal	Sub-acute	M	Urine porphyrins
	Amyloid	Axonal	Sub-acute to chronic	S/M	SPEP Nerve biopsy

A = autonomic; CIDP = chronic inflammatory demyelinating polyneuropathy; GGT = gamma-glutamyl transferase; HMSN = hereditary motor sensory neuropathy;
M = motor; OGTT = oral glucose tolerance test; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; S = sensory; SLE = systemic lupus erythematosus;
SPEP = serum protein electrophoresis
* Neuropathies of vascular etiology usually present as mononeuropathy multiplex
+ Neuropathies of immune etiology usually present as polyradiculopathy

Guillain-Barré Syndrome

Definition
- acute, rapidly evolving (evolving over 4 wk or less) demyelinating inflammatory polyradiculoneuropathy that often starts in the distal lower limbs and ascends

Etiology
- autoimmune attack and damage to peripheral nerve myelin
- usually preceded by viral/bacterial infections

Signs and Symptoms
- sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
- motor: weakness starting distally in legs and progressing proximally, areflexia
- autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction

Investigations
- CSF: albuminocytologic dissociation (high protein, normal WBC)
- EMG/NCS: conduction block, differential or focal (motor>sensory) slowing, decreased F-wave, sural sparing

Treatment
- IVIG or plasmapheresis, pain management, monitor vitals and vital capacity

Prognosis
- peak of symptoms at 2-3 wk, plateau or resolution at 4-6 wk
- 5% mortality (higher if require ICU), up to 15% have permanent deficits

In GBS, IVIG and plasmapheresis lead to more rapid improvement, less intensive care, and less ventilation, but do not change mortality or relapse rate

GBS is a neurological emergency due to risk of imminent respiratory failure

The most commonly identified antecedent infection in GBS is *Campylobacter jejuni*

Miller-Fischer Variant of GBS – Triad
Ophthalmoplegia, ataxia, areflexia

Neuromuscular Junction Disorders

Table 20. Common Disorders of the Neuromuscular Junction

	Myasthenia Gravis	Lambert-Eaton	Botulism
Ocular/Bulbar Paresis	+	–	++ (early)
Limb Weakness	+	+	+
Fatigability	+	+	+
Post-Exercise Enhancement	–	+	+
Reflexes	N	↓	↓
Anticholinergic Sx	–	+	++
Sensory Sx	–	–	–
Associated Conditions	Thymoma	Small cell carcinoma	GI signs and symptoms
Repetitive EMG Stimulation	Decremental response	Incremental response	↑ (rapid stimulation) ↓ (slow stimulation)

Neuromuscular Junction Disease

Typically feature prominent fatigability

Fatigability can be tested by holding the arms out or by holding the gaze in the upward position (especially in MG)

Muscle weakness due to fatigability will improve with rest and/or ice

Myasthenia Gravis

Etiology and Pathophysiology
- autoimmune disorder of the neuromusclar junction, commonly associated with acetylcholine receptor antibodies or muscle-specific kinase antibodies
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia

Epidemiology
- bimodal age of onset, 20s (mostly women) and 60s (mostly men)

Clinical Features
- fatigable, symmetric, or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
- ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
- symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
- respiratory muscle weakness may lead to respiratory failure

Investigations
- repetitive stimulation: decrement in amplitude >10%
- single fibre EMG: shows increased jitter (80-100% sensitivity)
- spirometry: forced vital capacity may be used to monitor adequacy of respiratory effort over time
- acetylcholine receptor antibody assay (50-90% sensitivity); muscle-specific kinase antibody may be used if seronegative for acetylcholine receptor antibody
- CT/MRI chest: screen for thymoma/thymic hyperplasia
- edrophonium (Tensilon®) test: assess for improvement over 2 min following edrophonium injection (no longer performed)

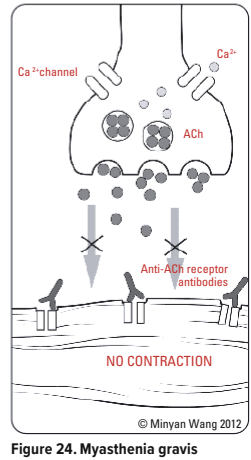


Figure 24. Myasthenia gravis

Treatment
- acetylcholinesterase inhibitors (e.g. pyridostigmine): first line treatment
- corticosteroids (e.g. prednisone): mainstay of treatment if acetylcholinesterase inhibitors not effective
- short-term immunomodulation (e.g. IVIG and plasmapheresis): for crisis
- long-term immunosuppression (e.g. azathioprine, cyclophosphamide, mycophenolate): can be used as steroid-sparing therapy
- newer medications that are more disease specific: Eculizumab (complement inhibitor), Efgartigimod (neonatal Fc receptor blocker)
- thymectomy: option in non-thymomatous acetylcholine receptor antibody-positive generalized MG (85% remission rate)

Prognosis
- 30% eventual spontaneous remission
- with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

Lambert-Eaton Myasthenic Syndrome

Etiology and Pathophysiology
- autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased acetylcholine release at the neuromuscular junction
- 50-66% are associated with small cell carcinoma of the lung

Clinical Features
- weakness of skeletal muscles without sensory or coordination abnormalities, proximal and lower muscles more affected
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and extraocular muscles affected in 25% (vs. 90% in MG)
- prominent anticholinergic autonomic symptoms (dry mouth>impotence>constipation>blurred vision)

Investigations
- rapid (>10 Hz) repetitive nerve stimulation: incremental response
- anti-P/O-type voltage-gated calcium channel antibodies: are present in 85-95% of patients with LEMS
- EMG: typically normal in LEMS
- edrophonium test: no response
- EMG: incremental response with exercise
- screen for malignancy, especially small cell lung cancer

Treatment
- tumour removal
- increase acetylcholine concentration at synaptic cleft
  - increase acetylcholine release (3,4-diaminopyridine)
  - decrease acetylcholine degradation (pyridostigmine)
- immunomodulation: corticosteroids, plasmapheresis, IVIG

Botulism

Etiology and Pathophysiology
- caused by a toxin produced by spores of Clostridium botulinum bacteria, which can enter through wounds or by ingestion
- infantile botulism is the most common form and is usually from ingestion of honey or corn syrup

Clinical Features
- occur 6-48 h after ingestion
- bilateral cranial neuropathies: ptosis, extraocular muscle weakness, dilated poorly reactive pupils, dysarthria, jaw weakness, dysphagia
- symmetric descending weakness with paralysis and absent/decreased reflexes
- autonomic dysfunction: nausea, orthostatic hypotension, constipation (paralytic ileus), bladder distension
- anticholinergic symptoms: dry mouth, constipation, urinary retention
- pattern of paresis often starts with GI symptoms → extraocular muscle weakness → dysphagia → limbs and respiratory involvement
- without prompt treatment, respiratory muscle weakness can lead to respiratory failure

Investigations
- blood test for toxin, stool culture
- CT/MRI to rule out intracranial lesion (normal in botulism)

Treatment
- botulinum anti-toxin: good prognosis with prompt treatment
- supportive therapy as required (monitor respiratory status and assess need for intubation)

Tensilon® is a drug that inhibits acetylcholinesterase. While it can improve muscle function immediately in MG, it is ineffective in a cholinergic crisis. Although it is no longer available for use, if it is administered, it is crucial to have a crash cart nearby, as respiratory difficulty and/or bradycardia may occur.

Randomized Trial of Thymectomy in Myasthenia Gravis
NEJM 2016;375:511-22
Purpose: To compare the efficacy of thymectomy plus prednisone vs. prednisone alone in the treatment of MG
Methods: 126 patients with generalized nonthymomatous MG (clinical class II-IV disease <5 years duration and elevated acetylcholine receptor antibodies) received extended transsternal thymectomy plus alternate-day prednisone or alternate-day prednisone alone.
Results: Over 3 years, thymectomy was associated with a lower time-weighted average quantitative MG score as compared to prednisone alone (6.15 vs. 8.99, P<0.001), and a lower average requirement for alternate-day prednisone (44 mg vs. 60 mg, P<0.001). Immunosuppression was required by fewer patients in the thymectomy group (17% vs. 48%, P<0.001); they were also hospitalized less frequently for exacerbations (9% vs. 37%, P<0.001).
Conclusion: In patients with nonthymomatous MG, thymectomy improved clinical outcomes.

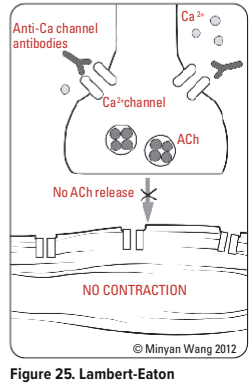


Figure 25. Lambert-Eaton myasthenic syndrome

Myopathies

Table 21. Myopathies

	Etiology	Key Clinical Features	Key Investigations
Inflammatory	Polymyositis (see Rheumatology, RH16)	Proximal muscle weakness Myalgias Nasopharyngeal involvement	↑ creatine kinase Biopsy: endomysial infiltrates, necrosis
	Dermatomyositis (see Rheumatology, RH16)	Proximal muscle weakness Myalgias Characteristic rashes Can be paraneoplastic	↑ creatine kinase Biopsy: perifascicular atrophy
	Sarcoidosis	See Respirology, R16	ACE level Biopsy: granulomas
	Inclusion body myositis	Weak quadriceps and deep finger flexors	↑ creatine kinase Biopsy: inclusion bodies
Endocrine	Thyroid (↑ or ↓) Cushing's syndrome Parathyroid (↑ or ↓)	See Endocrinology, E25	TSH Serum cortisol Calcium panel
Toxic	Medication	Medication or toxin history	Toxicology screen
	Critical illness myopathy	ICU patient Hx steroids and nondepolarizing paralyzing agents Failure to wean from ventilation	Biopsy: selective loss of thick myosin filaments
Infectious	Parasitic, bacterial, or viral	Myalgias Inflammatory myopathy	↑ myoglobin
Hereditary Dystrophy	Duchenne (see Medical Genetics, MG8)	Early onset (Duchenne and Becker)	Dystrophin analysis: absent Genetic testing
	Becker	Progressive proximal muscle weakness Calf pseudohypertrophy	Dystrophin analysis: reduced Genetic testing
	Myotonic dystrophy	Distal myopathy Myotonia Genetic anticipation	Genetic testing
Hereditary Metabolic	McArdle's	Exercise-related myalgias, cramping, and myoglobuminuri	↑ lactate ↑ serum/urinary myoglobin post-exercise
Hereditary Periodic Paralysis	"Channelopathy"	Episodic weakness Normal between attacks	Normal, ↑ or ↓ K^+
Hereditary Mitochondrial	MERRF (mitochondrial encephalopathy with ragged red fibres)	Myoclonus, generalized seizures, dementia, myopathy	Biopsy: ragged red fibres Increased lactate
	MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes)	Paediatric onset, stroke-like symptoms, episodic vomiting, dementia	
	Kearns Sayre	Progressive ophthalmoplegia, retinal pigment degeneration, cardiac conduction abnormalities	

MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF: mitochondrial encephalomyopathy with ragged red fibres
CK: creatine kinase

Myotonic Dystrophy Type 1

Etiology and Pathophysiology

- unstable trinucleotide (CTG) repeat in myotonic dystrophy kinase gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms, autosomal dominant

Epidemiology

- most common adult muscular dystrophy, prevalence 3-5 in 100000

Clinical Features

- appearance
  - ptosis, facial weakness, frontal baldness (including women), atrophy of facial, levator palpebrae, and masticatory muscles giving a drooping/dull appearance
- physical exam
  - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
  - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
  - cardiac: 90% have conduction defects (1° heart block; atrial arrhythmias)

- respiratory: hypoventilation 2° to muscle weakness
- ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
- other: DM, infertility, testicular atrophy
- EMG: electrical myotonia (waxing and waning discharges, sound like "dive-bomber")

Treatment
- management of myotonia: mexiletine, phenytoin

Prognosis
- varies with age of onset and number of CTG repeats
- no cure, progressive, death usually around 50 yr

Pain Syndromes

Pinprick sensation mediated by Aδ fibres

Pain due to tissue damage is mediated by C fibres

Definitions
- nociceptive pain: pain arising from stimulus causing potential or actual non-neural tissue injury
- neuropathic pain: pain arising from lesion or disease affecting the somatosensory system
- spontaneous pain: unprovoked burning, shooting, or lancinating pain
- paresthesia: spontaneous abnormal non-painful sensation (e.g. tingling)
- dysesthesia: evoked pain with inappropriate quality or excessive quantity
- allodynia: pain response to a non-noxious stimulus
- hyperalgesia: exaggerated pain response to a noxious stimulus

WHO Pain Ladder
Mild Pain: Non-opioid (acetaminophen and/or NSAID) ± adjuvant
Moderate Pain: Opioid for mild to moderate pain (codeine/oxycodone) + non-opioid ± adjuvant
Severe Pain: Opioid for moderate to severe pain (morphine/hydromorphone) + non-opioid ± adjuvant

Non-Pharmacological Management
- physical (PT, acupuncture, chiropractic manipulation, massage)
- psychoeducational (cognitive behavioural therapy,, family therapy, education, psychotherapy)

Pharmacological Management
- combination multi-modal therapy is important
- primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches, and arthritis), opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympatholytics (phenoxybenzamine), α2-adrenergic agonists (clonidine)

Axonal regeneration is directed by intact nerve sheaths. If the nerve sheath is damaged, axons grow without direction, become tangled, and form a neuroma. This can result in ectopic electrical impulses and neuropathic pain

Surgical Management
- peripheral ablation: nerve blocks, facet joint denervation
- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy, or dorsal root entry lesion
- DBS or dorsal column stimulation

Neuropathic Pain

Epidemiology
- affects up to 6% of people (2 million Canadians)

Symptoms and Signs
- hyperalgesia, allodynia
- subjectively described as burning, heat/cold, pricking, electric shock, perception of swelling, numbness
- can be spontaneous or stimulus evoked, distribution may not fall along classical neuro-anatomical lines
- associated issues: sleep difficulty, anxiety/stress/mood alteration

Causes of Neuropathic Pain
- **sympathetic**: complex regional pain syndrome
- **non-sympathetic**: damage to peripheral nerves
  - systemic disease: DM, thyroid disease, renal disease, rheumatoid arthritis, MS
  - nutritional/toxicity: alcoholism, pernicious anemia, chemotherapy
  - infectious: post-herpetic, HIV
  - trauma/compression: nerve entrapment, trigeminal neuralgia, post-surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy
- **central**: abnormal CNS activity
  - phantom limb, post spinal cord injury, post stroke, MS

Treatment
- identify/treat underlying cause
- **pharmacotherapy**
  - stepwise approach (Canadian Pain Society, 2014)
    - 1st line: gabapentinoids, TCA, serotonin and norepinephrine reuptake inhibitor (SNRI)
    - 2nd line: tramadol, opioid analgesics
    - 3rd line: cannabinoids
    - 4th line: methadone, anticonvulsants (lamotrigine, lacosamide), tapentadol, botulinum toxin

- **common non-pharmacologic therapies**
  - neuropsychiatry: cognitive behavioural therapy,, psychotherapy
  - rehabilitation: physiotherapy
- **surgical therapies**: dorsal column neurostimulator, DBS (thalamus)

Trigeminal Neuralgia

Clinical Features
- recurrent episodes of sudden onset, excruciating, unilateral, paroxysmal, shooting "electric" pain in trigeminal root territory (V3>V2>>V1)
- may have normal sensory exam (if abnormal, think of secondary or structural cause)
- pain lasts s/min over d/wk, may remit for wk/mo
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up

Etiology
- classical: compression of trigeminal nerve by tortuous blood vessel (usually superior cerebellar artery)
- secondary: cerebellopontine angle mass, MS
- idiopathic

Epidemiology
- F>M; usually middle-aged or elderly

Diagnosis
- clinical diagnosis
- MRI brain to rule out vascular lesion, intracranial mass, MS

Treatment
- first line: carbamazepine or oxcarbazepine
- second line: baclofen or lamotrigine
- for medically-refractory classical trigeminal neuralgia, consider microvascular decompression
- other neurosurgical options for medically refractory trigeminal neuralgia: trigeminal ganglion percutaneous technique, gamma knife radiosurgery, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression
- narcotics not generally recommended

Postherpetic Neuralgia

Clinical Features
- pain persisting in the region of a cutaneous outbreak of herpes zoster
- constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
- distribution: thoracic, trigeminal, cervical, lumbar, sacral
- associated symptoms: impaired sleep, decreased appetite, decreased libido

Herpes Zoster of Trigeminal Nerve
Typically involves V1 (ophthalmic division)
Hutchinson's Sign
Tip of nose involvement predicts corneal involvement

Etiology and Pathogenesis
- destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

Epidemiology
- incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
- risk factors: older age, greater acute pain, greater rash severity

Prevention
- varicella zoster vaccine (Varivax®) in childhood reduces incidence of varicella zoster
- herpes zoster vaccine (Zostavax® or Shingrix®) reduces incidences of shingles, postherpetic neuralgia, and other herpetic sequelae
  - Zostavax® is a live vaccine, recommended for patients ≥60 yr
  - Shingrix® is a recombinant vaccine, recommended for patients ≥50 yr (more efficacious than Zostavax®)

Treatment
- medical: TCA (e.g. amitriptyline), anticonvulsants (e.g. pregabalin, gabapentin), analgesia (e.g. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  - early treatment of acute herpes zoster with antivirals (longer-acting famciclovir and valacyclovir more effective)
  - treatment of herpes zoster with corticosteroids does not decrease PHN
- surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus

Painful Diabetic Neuropathy

- see Endocrinology, E16

Approach
- determine if pain is neuropathic or vascular
- more likely neuropathic if pain is present at rest and improves with walking, pain is sharp/tingling, more in feet → calves

Treatment
- level A: pregabalin
- level B: venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, rarely opioids, capsaicin

Complex Regional Pain Syndrome

Definition
- regional pain characterized by pain, swelling, skin changes, and limited range of motion
- often disproportionate to the inciting event (e.g. fracture, stroke), typically lasting 4-6 wk

Diagnosis
- clinical diagnosis consistent with the Budapest Criteria:
    1. continuing regional pain disproportionate to an inciting event
    2. patient must have symptoms in 3 of the 4 categories, and must have signs in 2 of the 4 categories (a sign must be observed at the time of diagnosis):
        - sensory: hyperesthesia and/or allodynia
        - vasomotor: temperature and/or skin colour asymmetry
        - sudomotor/edema: edema, sweating changes, and/or sweating asymmetry
        - motor/trophic: decreased range of motion, motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nail)
    3. absence of any other diagnosis that would better explain the signs or symptoms
- bone scintigraphy ≤5 mo of symptom onset may support diagnosis (negative test does not rule it out)
- MRI may help rule out other causes of regional pain if indicated

Classification
- type I (reflex sympathetic dystrophy): minor injuries of limb or lesions in remote body areas precede onset of symptoms
- type II (causalgia): injury of peripheral nerves precedes the onset of symptoms

Prevention
- early mobilization after injury/infarction

Treatment
- goal of treatment is to facilitate function
- conservative treatment: education, support groups, PT, OT, smoking cessation
- medical: topical capsaicin; TCA; NSAID; tender point injections with corticosteroid/lidocaine; gabapentin/pregabalin/lamotrigine; calcitonin or bisphosphonates; oral corticosteroids
- surgical: paravertebral sympathetic ganglion blockade
- refer to pain management clinic

Headache

• see Emergency Medicine, ER16 and Family Medicine, FM36

Clinical Approach

• **history**
- pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g. worse in AM, worse with bending/coughing/Valsalva)
- associated symptoms: visual changes, change in mental status, N/V, fever, meningismus, photophobia, phonophobia, temporomandibular popping/clicking, jaw claudication, neurological symptoms
- precipitating/alleviating factors (triggering factors, analgesics), medications (especially nitrates, calcium channel blockers, NSAIDs, anticoagulants), PMHx, FHx
- red flags (possible indications for CT scan/further investigation) "SNOOP4": Systemic symptoms or 2° risk factors (fever, weight change, immunocompromised); Neurological symptoms; Onset sudden ('thunderclap'); Older age (especially new-onset headache >50 yr); Pattern change; Positional (worse standing vs. worse supine); Precipitated by Valsalva or cough; Pregnancy-CSVT/IIH/Preeclampsia

• **physical exam**
- vitals (including BP and temperature), Jolt accentuation/Kernig's/Brudzinski's, MSK examination of head and neck
- HEENT: fundi (papilledema, retinal hemorrhages), red eye, temporal artery tenderness, sinus palpation, TMJ
- full neurological exam (including LOC, orientation, pupils (symmetry), and focal neurological deficits)
- red flags: papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

Classification

• primary (cause disability but no brain damage or death)
- tension, migraine, cluster, autonomic cephalgias, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)

• secondary (medical emergency; can lead to irreversible brain damage or death)
- cervical osteoarthritis, TMJ syndrome, SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN, or IIH), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-eclampsia, post-LP, drugs/toxins (e.g. nitroglycerin use and analgesia withdrawal)

Table 22. Headaches – Selected Primary Types

	Tension-Type	Migraine	Cluster
Prevalence	30-40%	≈10-20%	<1%
Age of Onset	15-40	10-30	20-40
Sex Bias	F>M	F>M	M>F
Family History	None	+++	+
Location	Bilateral frontal Nuchal-occipital	Unilateral > bilateral (in adults especially) Fronto-temporal	Retro-orbital Supra-orbital Temporal
Duration	Minutes-days	Hours-days	10 min-2 h
Onset/Course	Gradual, worse in PM Episodic or chronic	Gradual, worse in PM; can also be acute	Daily attacks for weeks to months; more common early AM or late PM
Quality	Band-like, constant	Pulsating, throbbing	Constant, aching, stabbing
Severity	Mild-moderate (does not wake you up from sleep)	Moderate-severe	Severe (wakes from sleep)
Triggers/Provoking	Depression Anxiety Noise Hunger Sleep deprivation	Noise/light Caffeine/alcohol Hunger Stress Sleep deprivation	Light EtOH
Palliating	Rest	Rest	Walking around
Associated Symptoms	No vomiting No photophobia	N/V Photo/phonophobia/osmophobia ± Aura	Red watery eye Eyelid, forehead swelling Nasal congestion or rhinorrhea Unilateral Horner's
Management	Non-pharmacological: Eliminating known triggers Healthy lifestyle: sleep, diet (protein for breakfast), exercise, hydration, be aware of technology use, vitamin/minerals Psychological counseling Physical modalities (e.g. heat, massage) Pharmacological Vitamins/minerals - Magnesium citrate, Riboflavin (Vitamin B2), Coenzyme Q10, Melatonin if insomnia or difficulty falling asleep Simple analgesics: Tylenol, NSAIDs	Acute Rx/Abortive: NSAIDs Triptans Ergotamine Valproate Anti-emetics CGRP Antagonists Prophylaxis/Preventive: TCA Calcium channel blockers Anticonvulsants β-Blockers Botox	Acute Rx O2 Sumatriptan (nasal or injection) Prophylaxis Verapamil Lithium Methysergide Prednisolone Valproate CGRP antibody

If CT is negative but clinically there is suspicion of SAH or meningitis, perform an LP

Headache DDx

ER VISIT
Eye (acute angle closure glaucoma, sinusitis)
Recurrent/Chronic (migraine, tension, cluster, temporomandibular joint disease, cervical osteoarthritis)
Vascular (SAH, ICH, temporal arteritis)
Infectious (meningitis, encephalitis)
Systemic (anemia, anoxia, CO, pre-eclampsia)
ICP (mass/abscess, HTN encephalopathy, IIH)
Trauma (epidural hematoma, subdural hematoma, concussion)

Trial of Galcanezumab in Prevention of Episodic Cluster Headache
NEJM 2019;381:132-41
Purpose: To investigate the efficacy and safety of galcanezumab as a preventive treatment for cluster headache.
Methods: 106 patients who had min. one attack every other day, min. four total attacks, and max. eight attacks/d, plus a history of cluster headache periods lasting min. 6 wk, received 300 mg galcanezumab or placebo, administered SC at baseline and 1 mo.
Results: After 3 wk, the mean reduction in the weekly frequency of cluster headache attacks was 8.7 attacks in the galcanezumab group vs. 5.2 in the placebo group (difference, 3.5/wk; 95% CI, 0.2-6.7; P=0.04), and the proportion of patients who had a reduction of ≥50% in headache frequency was 71% and 53%, respectively (P=0.046). Incidence of adverse events were similar in both groups.
Conclusion: Galcanezumab reduced the weekly frequency of attacks of episodic cluster headache.

Antiepileptics in Migraine Prophylaxis: An Updated Cochrane Review
Cephalalgia 2015;35:51-62
Purpose: To review the evidence for anticonvulsants in migraine prophylactics.
Study: Systematic meta-analysis of 37 published and 3 unpublished prospective, controlled trials of regular use of anticonvulsants to prevent migraines and/or improve quality of life related to migraines.
Results: Sodium valproate and topiramate were associated with a reduction of 4 d and 1 d of headache per month, respectively, and patients taking either drug were more than 2 times as likely to experience greater than 50% reduction in headache frequency, vs. placebo. Neither drug was associated with undue rates of adverse events, though higher doses of topiramate were associated with increased adverse events. There is insufficient evidence of efficacy with other antiepileptic drugs, including gabapentin, for migraine prophylaxis.
Conclusions: Daily sodium valproate 400 mg and topiramate 50 mg are well tolerated and effective in prophylactic treatment of migraine headache in adults.

Table 23. Prophylactic Management of Migraine Headaches

Class	Drug	Evidence	Contraindications	Side Effects
β-blockers	Propranolol	A	Asthma, DM (mask hypoglycemia) CHF	Fatigue Depression Light-headedness
	Timolol	A		
	Metoprolol	B		
TCA	Amitriptyline	A	Heart disease, glaucoma Avoid in elderly	Sedation Dry mouth Weight gain Light-headedness
	Nortriptyline	C		
CCBs	Flunarizine	A	Depression, obesity	Weight gain, depression, PD (rare)
	Verapamil	B	Heart disease	Weight gain (4.5-9 kg), constipation
AED	Valproate	A	Liver, pancreatic disease	Weight gain, elevated liver enzymes/ hyperammonemia, tremor, alopecia, teratogenic: neural tube defect
	Topiramate	A	Renal disease	Paresthesia, acute angle-closure glaucoma, weight loss, cognitive: memory loss, difficulty concentrating, renal stone (rare)

Table 24. Headaches – Selected Serious but Rare Secondary Types

	Meningeal Irritation	Increased ICP	Temporal Arteritis
Age of Onset	Any age	Any age	>60 yr
Location	Generalized	Any location	Temporal
Onset/Course	Meningitis: hours-days SAH: thunderclap onset	Gradual; worse nocturnal and AM	Variable
Severity	Severe	Severe	Variable, can be severe
Provoking	Head movement	Lying down Valsalva Head low Exertion	Jaw claudication
Associated Symptoms	Neck stiffness Photophobia Focal deficits (e.g. CN palsies)	N/V Focal neurological symptoms Decreased LOC	Polymyalgia rheumatica Visual loss
Physical Signs	Kernig's sign Brudzinski's sign Meningismus	Focal neurological symptoms Papilledema	Temporal artery changes: firm, nodular, incompressible, tender
Management	CT/MRI with gadolinium, LP, antibiotics for bacterial meningitis	CT/MRI and treatment to reduce pressure See Neurosurgery, NS6 and NS7	Prednisone See Rheumatology, RH22
Etiology	Meningitis, SAH	Tumour, CSVT, IIH, malignant HTN	Vasculitis (GCA)

Migraine

Definition

- ≥5 attacks fulfilling each of the following criteria
  - 4-72 h in duration
  - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  - 1 of the following: N/V, photophobia/phonophobia/osmophobia
  - not better accounted for by another diagnosis

Migraine auras can mimic other causes of transient neurological deficits (e.g. TIAs and seizures)

Epidemiology

- 18% females, 6% males; frequency decreases with age (especially at menopause)
- in pre-pubertal children, more commonly seen in males; post-pubertal, more commonly seen in females

"Menstrual Migraine" Subtype
Migraine headache that is associated with the onset of menstruation – usually 2 d before to 3 d after the onset of menstrual bleeding

Etiology and Pathophysiology

- 20% of migraines are associated with aura, caused by depolarizing wave of "cortical spreading depression" across the cerebral cortex (e.g. visual symptoms due to wave through occipital cortex); possible association with vasoconstriction/dilation
- significant genetic contribution
- triggers: stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrites (e.g. processed meats)

Signs and Symptoms

- stages of uncomplicated migraine
  1. prodrome (h to d before headache onset)
  2. aura
  3. headache
  4. postdrome

- aura
  - self-resolving symptom of focal cerebral dysfunction lasting <60 min
  - e.g.: visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots), unilateral paresthesia and numbness or weakness, aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
- classification of migraines
  - common migraine: no aura
  - classic migraine: with aura (headache follows reversible aura within 60 min)
  - complicated migraine: with severe/persistent sensorimotor deficits
  - examples: basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered LOC), hemiplegic/hemisensory migraine, ophthalmoplegic migraine
  - acephalgic migraine (i.e. migraine equivalent): aura without headache
  - status migrainosus: single attack lasting longer than 72 h

Treatment

- avoid triggers
- mild to moderate migraine
  - 1st line: NSAIDs (ibuprofen, naproxen)
- moderate to severe migraine
  - triptans (most effective), ergots (dihydroergotamine, dihydroergotamine mesylate (DHE))
- for chronic migraine, consider migraine prophylaxis: anticonvulsants (valproate, topiramate), TCA (amitriptyline, nortriptyline), propranolol, calcium channel blocker (verapamil)
- medication overuse (use of triptans/opioids/combination analgesics for ≥10 d/mo, or use of NSAIDs for ≥15 d/mo) can lead to medication-overuse headaches

The oral contraceptive pill is contraindicated with complicated migraine due to risk of stroke
- Can still use non-estrogen based forms of birth control (e.g. copper IUD, Depo-provera shot)

If patient presents to ED with severe migraine and N/V – consider treating with IV fluids and anti-emetics (chlorpromazine, prochlorperazine)

Sleep Disorders

Sleep Overview

Recommendations

- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many older patients have reduced sleep as a consequence of underlying sleep disorders

Sleep Architecture

- polysomnography measures: EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG

Table 25. Sleep Stage Characteristics

	EEG	EOG	Muscle Tone	Other Characteristics
Waking State	Alpha waves: high frequency (8-12 Hz), moderate amplitude Beta waves: frequency >13 Hz, low amplitude	Rapid, blinking	High	
Stage N1 (~5%)	<50% Alpha waves (see above), mixed with slow wave activity (theta, 4-7 Hz)	Slow, roving eye movements	High, but gradually dropping	Marker for very light quality sleep or sleep disruption
Stage N2 (~50%)	K complexes (high voltage negative and positive discharges) with sleep spindles (12-14 Hz) are central and midline	Still	High	
Stage N3 (previously 3 and 4)/Slow Wave/Delta Sleep (~20%)	Delta waves: low frequency (~2 Hz), high voltage (>75 μV)	Still	Low	Homeostatic sleep Reduced BP, HR, cardiac output, RR Growth hormone release
Rapid Eye Movement (REM) (~25%)	Sawtooth waves, mixed frequency, low voltage	Rapid eye movements	Very low	Irregular respiration HR variation Classical dreaming state

Elements of Sleep History
Initiation of sleep
Events prior to bed
Lights
Latency (estimated)
Restless legs
Hallucinations
Maintaining sleep
Number of nighttime awakenings
Sleep walking/talking
Snoring/gasping
Dreams/nightmares
Consequences of sleep
Restorative
Morning headache
Falling asleep in inappropriate setting

Drug Effects on Wakefulness and Sleep

Antihistamines increase sleepiness

Stimulants (e.g. caffeine; an adenosine receptor antagonist) increase arousal and wakefulness

Benzodiazepines reduce amount of slow wave sleep and cause sleepiness

Antidepressants (TCA/MAOI/SSRI) reduce amount of REM sleep and prolong REM latency

EtOH may hasten sleep onset but is associated with increased nighttime arousals and poor sleep efficiency

Avoid sleep medications (especially in elderly patients) due to increased risk of falls, pseudodepression, and memory loss

Coma

- see Neurosurgery, NS40

Insomnia

Definition
- difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep

Types
- sleep state misperception, psychophysiologic insomnia (learned sleep-preventing associations – i.e. clock watching), idiopathic (lifelong difficulty)
- secondary causes
  - psychiatric disorders (80% of psychiatric patients): i.e. depression and anxiety (see Psychiatry, PS12and PS16)
  - neurologic disorders: i.e. neurodegenerative disease, epilepsy, neuromuscular disorders
  - sleep disorders: i.e. restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
  - medical conditions: i.e. cardiorespiratory (COPD/heart failure), gastroesophageal reflux disease, pain (arthritis, fibromyalgia, cancer)
  - drugs/toxins: i.e. caffeine, EtOH, stimulants, antidepressants, corticosteroids, sedative withdrawal
  - fatal familial insomnia: i.e. rare genetic prion protein mutation causing autonomic dysfunction
  - pregnancy

Treatment
- sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, cognitive behavioural therapy, melatonin

Sleep Apnea

- see Respirology, R29

Definition
- disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence (or drowsiness)

Epidemiology
- >6% of the Canadian population
- risk factors and associated conditions: older age, obesity, male sex, craniofacial and upper airway abnormalities
- significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)

Types
- obstructive sleep apnea; etiology: collapse of airway due to low muscle tone in deep and REM sleep
- central sleep apnea: no effort to breath >10s; etiology: heart failure, opiates, brainstem pathology, myotonic dystrophy
- mixed apnea: combination of both central and obstructive sleep apnea

Diagnosis
- PSGs: home sleep apnea testing, in-hospital testing
  - apnea-hypopnea index (AHI) ≥5

Treatment
- continuous positive airway pressure (CPAP), weight loss, positional therapy (e.g. avoidance of supine sleep), dental devices, surgery (rare), ensure driving safety

Restless Legs Syndrome

- urge to move legs accompanied by uncomfortable sensations that begin or worsen with rest, is partially or totally relieved with movement, and is worse in evening/night
- 90% also have periodic limb movement disorder
- associated with iron deficiency, neuropathy, PD, EtOH, pregnancy, end-stage renal disease

Treatment
- iron supplementation if iron deficient
- gabapentinoids (pregabalin, gabapentin)
- dopamine agonists (pramipexole, rotigotine)
- benzodiazepines (usually clonazepam)
- opioids, if medically refractory

Periodic Limb Movement Disorder

- involuntary, jerking movements of the legs during sleep
- diagnosed with polysomnography
- 50% also have restless legs syndrome
- similar associated factors and treatment as restless legs syndrome

Narcolepsy

Definition
- excessive daytime sleepiness (all narcolepsy), cataplexy (loss of muscle tone with emotional stimuli, pathognomonic), sleep paralysis (unable to move upon wakening), hypnagogic and hypnopompic hallucinations (vivid hallucinations while falling asleep or waking up, respectively)

Epidemiology
- prevalence 1 in 2000, onset in adolescence/early adulthood; life-long disorder

Etiology
- presumed autoimmune attack on orexin/hypocretin system, post head injury, MS, hypothalamic tumours; rarely familial

Diagnosis
- based on clinical history and multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps

Treatment
- sleep hygiene and scheduled brief naps, restricted driving
- alerting agents: modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
- anticataplectic: TCAs, SSRIs, sodium oxybate

Parasomnias

Definition
- unusual behaviours in sleep with clinical features appropriate to stage of sleep

Etiology
- in elderly, REM sleep behaviour disorder may be associated with PD; in children, slow wave sleep arousals (sleep walking) may be associated with sleep-disordered breathing

Diagnosis
- clinical history in children, PSG in adults to exclude nocturnal seizures

Treatment
- behavioural management (safety, adequate sleep), clonazepam for REM sleep behaviour, tonsillectomy if appropriate in children

Central Nervous System Infections

- see Infectious Diseases, ID17

Spinal Cord Syndromes

- see Neurosurgery, NS34

Stroke

Terminology

- stroke: focal cerebral, spinal, or retinal infarction in a defined vascular distribution
  - infarction is permanent tissue injury (confirmed by neuroimaging)
- TIA: transient (<24 h), episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction on CT or MRI
  - may present with amaurosis fugax (transient monocular painless vision loss)

Pathophysiology

- two major types: ischemic (~80%) and hemorrhagic (~20%)

1. ischemic

- arterial thrombosis: thrombus formation in artery (local/in situ)
  - large vessel: stenosis or occlusion of the internal carotid artery, vertebral artery, basilar artery, or anterior/middle/posterior cerebral arteries
    - mechanism: insufficient blood flow beyond lesion (hemodynamic stroke)
    - underlying processes: atherosclerosis (most common cause), dissection, and vasculitis
  - small vessel/lacunar
    - mechanism: chronic HTN and DM cause vessel wall thickening and decreased luminal diameter
    - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule, and thalamus)
- cardioembolic: blockage of cerebral arterial blood flow due to thrombus originating from a cardiac source
  - atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
- systemic hypoperfusion (global cerebral ischemia)
  - inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest, arrhythmia, or MI)
  - primarily affects watershed areas (between the major cerebral arterial territories)

2. hemorrhagic

- intracerebral hemorrhage: bleeding into brain parenchyma
  - hypertensive (most common): due to chronic arteriosclerosis which predisposes vessels to focal necrosis and pseudoaneurysm formation eventually leading to intraparenchymal hemorrhage; most common sites are putamen, caudate nucleus, thalamus, cerebellum, and pons
  - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, aneurysms, vasculitis, drug use (cocaine or amphetamines)
- SAH, see Neurosurgery, NS22

Stroke Syndromes According to Vascular Territory

- anterior cerebral artery
  - contralateral leg weakness and/or sensory deficit
  - neurocognitive deficits (e.g. abulia, agitation, emotional lability)
- middle cerebral artery: most common artery involved in ischemic stroke
  - contralateral weakness and/or sensory deficit of face and arm
  - cortical sensory loss
  - may have contralateral homonymous hemianopsia or quadrantanopsia
  - if dominant (usually left) hemisphere: aphasia
  - if non-dominant (usually right) hemisphere: neglect, anosognosia
  - eye deviation towards the side of the lesion (away from the weak side)

Hypertensive Encephalopathy
Acute severe HTN (typically dBP >130 or sBP >200) can cause hypertensive encephalopathy. Abnormal fundoscopic exam (papilledema, hemorrhages, exudates, cotton-wool spots), focal neurologic symptoms, N/V, visual disturbances, seizures, and change in LOC

Consider transfer of acute stroke patient to a designated stroke centre for neuroprotective or thrombolytic therapy, and endovascular therapy if the patient is seen in first few hours

Early seizure activity occurs in 5-25% of patients after ICH

Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can have seizures, focal neurological deficits, or cranial nerve palsies. This is diagnosed with CT venography or magnetic resonance venography. Treatment is typically anticoagulation with heparin initially, then warfarin eventually

20-40% of patients with ischemic stroke may develop hemorrhagic transformation within 1 wk after the initial infarction
Can be exacerbated by reperfusion injury (distal migration of clot as it dissolves) naturally or by use of thrombolytic therapy, endovascular thrombectomy, or anticoagulation

Blood work should only delay treatment if patient is on anticoagulants, low platelet count suspected, abnormal electrolytes suspected, or any bleeding abnormality suspected

Suspect an alternate diagnosis if fever, decreased LOC, fluctuating symptoms, gradual onset, no focal neurological symptoms, and/or positive symptoms

Infarcted area of brain tissue can often appear normal on CT during the first several hours after stroke onset, especially if in posterior circulation

- posterior cerebral artery
  - contralateral homonymous hemianopsia or quadrantanopsia
  - midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  - thalamic findings: sensory loss, amnesia, decreased LOC
  - if bilateral: cortical blindness or prosopagnosia
  - hemiballism
- basilar artery
  - proximal (usually thrombosis): impaired eye movements, vertical nystagmus, reactive miosis, hemi- or quadriplegia, dysarthria, ataxia, locked-in syndrome, coma
  - distal (usually embolic, i.e. top of the basilar syndrome): somnolence, memory and behaviour abnormalities, oculomotor deficit
- posterior inferior cerebellar artery (lateral medullary or Wallenberg syndrome)
  - ipsilateral ataxia, ipsilateral Horner's syndrome, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, N/V, dysphagia, dysarthria, hiccups
- medial medullary infarct (anterior spinal artery, which can be associated with anterior cord infarct)
  - contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness
- lacunar infarcts (deep hemispheric white matter; involving deep penetrating arteries of middle cerebral artery, circle of Willis, basilar and vertebral arteries)
  - contralateral face, arm, leg hemiparesis
- common lacunar syndromes:
  - sensorimotor stroke: weakness and numbness of the face/arm/leg without other cortical signs (i.e. aphasia, apraxia, visual loss)
  - pure motor hemiparesis (posterior limb of internal capsule or ventral pons): contralateral arm, leg, and face
  - pure sensory loss (ventral thalamic): hemisensory loss
  - ataxic hemiparesis (ventral pons or internal capsule): ipsilateral ataxia and leg paresis
  - dysarthria-clumsy hand syndrome (ventral pons or genu of internal capsule): dysarthria, facial weakness, dysphagia, mild hand weakness, and clumsiness

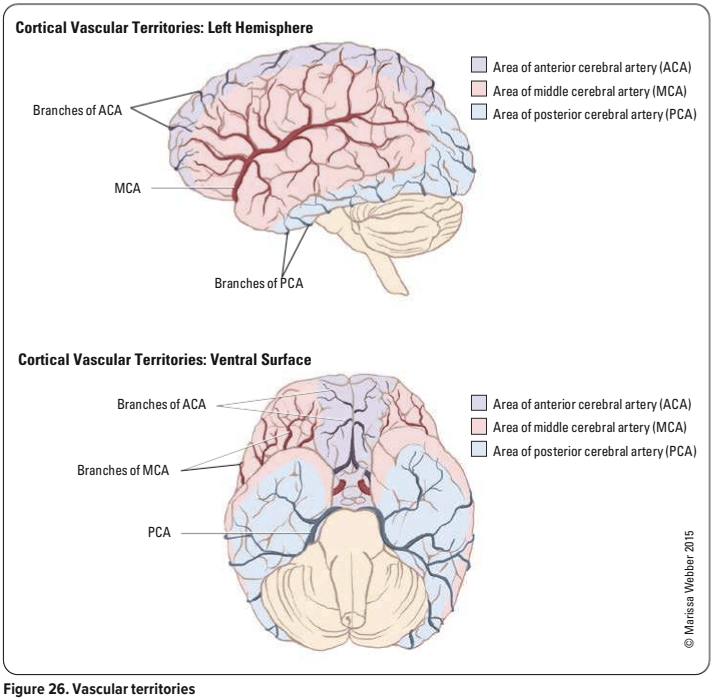

Cortical Vascular Territories: Left Hemisphere
Branches of ACA
MCA
Branches of PCA
Area of anterior cerebral artery (ACA)
Area of middle cerebral artery (MCA)
Area of posterior cerebral artery (PCA)
Cortical Vascular Territories: Ventral Surface
Branches of ACA
Branches of MCA
PCA
Area of anterior cerebral artery (ACA)
Area of middle cerebral artery (MCA)
Area of posterior cerebral artery (PCA)
© Marissa Webber 2015

Figure 26. Vascular territories

See Landmark Neurology Trials for more information on the ARISTOTLE trial. It details the efficacy of apixaban, an oral direct factor Xa inhibitor, in reducing the risk of stroke, as compared to warfarin.

The National Institute of Health Stroke Scale (NIHSS) is a standardized clinical examination that determines the severity of an acute stroke; it can also be used to monitor response to treatment over time

The scale uses 11 items that evaluate:

- LOC
- Visual system
- Motor system
- Sensory system
- Language abilities

Scoring (x/42):
0=no stroke
1-4=mild stroke
5-15=moderate stroke
16-20=moderate to severe stroke
21-42=severe stroke

ASPECTS: 10-Point Quantitative Score to Assess Ischemic Changes on CT

10/10 is normal and <4/10 signifies high-risk of bleed with tPA

Subtract 1 point for each of the following structures if abnormal within the ischemic hemisphere: caudate, lentiform, insula, internal capsule, middle cerebral artery 1, 2, 3, 4, 5, 6 regions

If tPA is given at stroke onset, delay acute antiplatelet/anticoagulation treatment by 24 h

Absolute Contraindications to tPA
Any source of active hemorrhage, any hemorrhage on brain imaging, any condition that could increase the risk of major hemorrhage after tPA administration

Assessment of Acute Ischemic Stroke

General Assessment

- ABCs, full vital sign monitoring, capillary glucose (Accu-Chek®), urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis), NIHSS
- LOC (knows age, month; obeys commands), dysarthria, dysnomia (cannot name objects)
- gaze preference, visual fields, facial palsy
- arm drift, leg weakness, ataxia
- sensation to pinprick, extinction/neglect
- history
  - onset: time when last known to be awake and symptom free
  - mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
- investigations
  - neuroimaging: non-contrast CT head (STAT) to rule out hemorrhage, MRI
  - vascular imaging: CT angiography (STAT), carotid Doppler ultrasound, magnetic resonance angiography, ECG
  - ECG, Holter monitor, transthoracic echocardiogram: to rule out cardioembolic causes such as atrial fibrillation
  - CBC, electrolytes, creatinine, partial thromboplastin time (PTT)/INR, blood glucose, lipid profile
- imaging (i.e. CT ± MR or CT angiography) signs of stroke
  - loss of cortical white-grey differentiation
  - sulcal effacement (i.e. mass effect decreases visualization of sulci)
  - hypodensity of parenchyma
  - insular ribbon sign
  - hyperdense middle cerebral artery sign
  - calculate ASPECTS score for CT

Treatment of Acute Ischemic Stroke

1. Neuroprotective Strategies

- BP, glucose, temperature control (exact targets will depend on clinical scenario)

2. Intravenous Thrombolysis

- tPA should be given within 4.5 h of acute ischemic stroke onset provided there are clinical indications and no contraindications to use (see sidebar)

3. Mechanical Thrombectomy

- early endovascular treatment of proximal anterior circulation occlusion has significant benefit on outcomes
  - ≤6 hr: with small-to-moderate ischemic core on CT
  - 6-24 hr: CT perfusion used to select patients who meet DAWN trial criteria
  - for basilar occlusions: weigh risks and benefits
- current standard of care is IV tPA + mechanical thrombectomy

4. Antiplatelet Therapy

- loading dose of antiplatelets at presentation of TIA or stroke if tPA not received (acute therapy)
  - loading dose of ASA: recommended dose 160 mg chewed
  - if patient intolerant to ASA, use another antiplatelet agent (e.g. clopidogrel 300 mg)
- secondary stroke prevention
  - if high risk TIA or minor stroke (NIHSS ≤4), load with ASA and clopidogrel and treat with dual antiplatelet therapy for 21 d (ASA 81 mg and clopidogrel 75 mg), followed by antiplatelet monotherapy

5. Acute Anticoagulant Therapy

- delay initiation/hold oral anticoagulation depending on size of infarct and presence of petechial/frank hemorrhage

Other Acute Management Issues

- avoid hyperglycemia which can increase the infarct size
- lower temperature if febrile (febrile stroke: think septic emboli from endocarditis)
- prevent complications
  - NPO if dysphagia (to be reassessed by SLP)
  - DVT prophylaxis if bed-bound
  - initiate rehabilitation early

Relative Contraindications to rtPA
Historical: history of ICH, stroke, or serious head/spinal trauma in the preceding 3 mo, major surgery in the preceding 14 d (risk varies by procedure), arterial puncture at a non-compressible site in the previous 7 d
Clinical: suspicious for SAH, suspicious for another non-ischemic acute neurological condition (e.g. post-ictal Todd's paralysis, focal neurological signs due to severe hypo- or hyperglycemia), elevated BP (sBP ≥180 mmHg, dBP ≥105 mmHg) refractory to treatment, current use of direct oral anticoagulant
Imaging: early signs of extensive infarction
Laboratory: ood glucose <2.7 mmol/L or >22.2 mmol/L, elevated activated partial thromboplastin time (aPTT), INR >1.7, platelet count <100 x 10^{3}mm^3

See Landmark Neurology Trials for more information on the DAWN trial. It details the efficacy and safety of endovascular thrombectomy performed more than 6 h after the onset of ischemic stroke in patients who were well 6-24 h earlier with a mismatch between clinical deficit and infarct.

See Landmark Neurology Trials for more information on the SPARCL trial. It details whether statins reduce the risk of stroke after a recent stroke or TIA.

Evaluating for Occult Atrial Fibrillation – CRYSTAL AF Trial
NEJM 2014:370;2478-86
Purpose: To investigate optimal methods for using ECG to detect atrial fibrillation after cryptogenic stroke.
Methods: 441 patients ≥40 yr with no evidence of atrial fibrillation during ≥24 h ECG monitoring received long-term monitoring with an insertable cardiac monitor (ICM) or conventional follow-up (control).
Results: Incidence of atrial fibrillation detection in the ICM group vs. the control group was 8.9% vs. 1.4% at 6 mo (hazard ratio, 6.4; 95% CI, 1.9-21.7; P<0.001), and 12.4% vs. 2.0% at 12 mo (7.3 (2.6-20.8); P<0.001), respectively.
Conclusion: Following cryptogenic stroke, ECG monitoring with ICM was more effective than conventional follow-up for detecting atrial fibrillation.

Carotid endarterectomy needs to be done within 2 wk of the ischemic event for the most benefit

Blood Pressure Control
- do not lower the blood pressure unless the HTN is severe
- antihypertensive therapy is withheld for 48-72 h (permissive hypertension) after non-thrombolysed ischemic stroke unless sBP >220 mmHg or dBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection (IV labetalol first-line if needed)
  - if patient receives tPA, target BP ≤180/105 mmHg
- acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
- most patients with an acute cerebral infarct are initially hypertensive but their BP will improve within 1-2 d

Stroke Rehabilitation
- individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

Primary and Secondary Prevention of Ischemic Stroke

Antiplatelet Therapy
- primary prevention
  - no firm evidence of a protective role for antiplatelet agents in low-risk patients without a prior stroke/TIA
- secondary prevention
  - initial choice: ASA, but other antiplatelet agents reasonable alternatives (clopidogrel or ASA/dipyridamole)
  - longer-term use of combined ASA and clopidogrel not recommended for secondary prevention unless there is an alternate indication (e.g. coronary drug-eluting stent requiring dual antiplatelet therapy), due to increased risk of bleeding and mortality

Carotid Stenosis
- primary prevention (asymptomatic)
- carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per yr; carotid endarterectomy reduces the risk of stroke by 1% per yr (but 5% risk of complications)
- secondary prevention (previous stroke/TIA in carotid territory)
  - carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%), as well as those with moderate stenosis (50-69%) but to a lesser degree (NASCET trial), see Vascular Surgery, VS9
- according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI, and death; however, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI

Atrial Fibrillation
- primary and secondary prevention with anticoagulation
  - classical risk stratification used CHADS2 score (0-6), but Stroke 2014 guidelines recommend that virtually all patients with atrial fibrillation without contraindication be anticoagulated
    - 0 (low-risk, 1.9% annual stroke risk): antiplatelet
    - 1 (intermediate risk, 2.8% annual stroke risk): anticoagulant or antiplatelet – patient specific decision
    - >2 (high-risk, 4-18.2% annual stroke risk): anticoagulant
  - anticoagulation therapy
    - warfarin (titrate to INR 2-3)
    - direct oral anticoagulants (DOAC): dabigatran (110 or 150 mg PO BID), apixaban (2.5 or 5 mg PO BID), rivaroxaban (15 or 20 mg PO once daily), or edoxaban (30 or 60 mg once daily) may be alternatives to warfarin and generally have a lower risk of ICH
- Praxbind® reversal agent for dabigatran if necessary
- Andexanet® reversal agent for apixaban and rivaroxaban if necessary
- do not use DOAC in patients with mechanical heart valves or AF with valvular heart disease

Hypertension
- primary prevention
  - targets: BP <140/90 mmHg (sBP <120 mmHg for high-risk without DM (SPRINT trial) or <130/80 mmHg for people with DM or renal disease)
  - ACE inhibitor: ramipril 10 mg PO once daily is effective in patients at high-risk for cardiovascular disease (HOPE trial)
- secondary prevention
  - combination of ACE inhibitor and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

CHADS2
Stroke risk stratification for patients with atrial fibrillation
CHF (1 point)
HTN sBP >160 mmHg/treated HTN (1 point)
Age >75 yr (1 point)
DM (1 point)
Prior Stroke or TIA (2 points)

ABCD^2 Score
To predict/identify individuals at high-risk of stroke following TIA
Age: 1 point for age >60 yr
Blood pressure (at presentation): 1 point for HTN (>140/90 mmHg at initial evaluation)
Clinical features: 2 points for unilateral weakness, 1 point for speech disturbance without weakness
Duration of symptoms: 1 point for 10-59 min, 2 points for >60 min
DM: 1 point
Stroke risk: 0-3: low-risk, 4-5: moderate risk, 6-7: high-risk

See Landmark Neurology Trials for more information on the SAMMPRIS trial. It compares the efficacy of percutaneous transluminal angioplasty and stenting (PTAS) to aggressive medical management in intracranial arterial stenosis.

Endovascular Thrombectomy after Large-Vessel Ischemic Stroke: A Meta-Analysis of Individual Patient Data from Five Randomized Trials
Lancet 2016;387:1723-1731
Purpose: To compare the efficacy of endovascular thrombectomy to standard medical care in patients with acute ischemic stroke due to occlusion of the proximal anterior circulation.
Study: A meta-analysis of individual patient data from 5 RCTs (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA).
Results: Data from 1287 individual patients (634 assigned to endovascular thrombectomy and 653 assigned to control) were analyzed. The number needed to treat to reduce disability for one patient by at least one level on the modified Rankin Scale, which measures disability and dependence in activities of daily living, was 2.6. Mortality at 90 d and risk of parenchymal hematoma and symptomatic ICH did not differ between the endovascular thrombectomy and control groups.
Conclusion: Most patients—irrespective of patient characteristics or geographical location—with acute ischemic stroke caused by occlusion of the proximal anterior circulation benefit from endovascular thrombectomy.

Hypercholesterolemia
- primary prevention
  - statins in patients with CAD or at high-risk for cardiovascular events, even with normal cholesterol (CARE trial)
- secondary prevention
  - target LDL <2 mmol/L (or 50% reduction in LDL); high dose atorvastatin (SPARCL trial) but lower doses may be adequate if intolerable

Type 1 and Type 2 Diabetes
- HbA1c <7%, fasting blood glucose 4-7 mmol/L, 2 h postprandial plasma glucose target 5-10 mmol/L

Smoking
- primary prevention: smoking increases risk of stroke in a dose-dependent manner
- secondary prevention: combination of pharmacological therapy and behavioural therapy should be considered in all smoking cessation programs; after smoking cessation, the risk of stroke decreases to baseline within 2-5 yr

Physical Activity
- beneficial effect of regular physical activity has a dose-related response in terms of intensity and duration of activity

Intracranial Hemorrhage

Definition
- intracranial bleeding into epidural space (epidural hematoma), subdural space (subdural hematoma), subarachnoid space (SAH), brain parenchyma (ICH), or ventricles (intraventricular hemorrhage)

Etiology
- head trauma, aneurysm, arteriovenous malformation, cavernous malformation, brain tumour, hemorrhagic stroke

Investigations
- general investigations: see *Assessment and Treatment of Acute Ischemic Stroke, N53*
- further investigations, when clinically indicated:
  - LP (if CT head negative and >6 h from headache onset)
  - may require cerebral angiogram if suspecting aneurysm or arteriovenous malformation
  - if typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion

Treatment
- medical
  - anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2020 Canadian Stroke Best Practice Guidelines suggest that sBP<140-160 mmHg for the first 24-48h post-ICH is reasonable
  - ICP lowering medical management (if necessary): see Neurosurgery, NS8
- surgical: see Neurosurgery, NS8

Neurocutaneous Syndromes
- see Pediatrics, P89

Multiple Sclerosis

Definition
- an autoimmune chronic inflammatory disease of the CNS characterized by relapsing-remitting or progressive neurologic symptoms due to inflammation, demyelination, and axonal degeneration

Epidemiology
- global prevalence ~2.8 million
- onset 17-35 yr; F:M=3:1
- genetic
  - polygenetic: the HLA-DRB1 gene has been demonstrated to be a genetically susceptible area
  - 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
- environmental
  - MS is more common in regions with less sun exposure and lower stores of vitamin D (Europe, Canada, US, New Zealand, Southeast Australia)
  - MS has also been linked to certain viruses (e.g. EBV)

ACE Inhibitor in Stroke Prevention – HOPE Trial
NEJM 2000;342:145-153
Study: Randomized, blinded, placebo-controlled trial. Mean follow-up 5 yr.
Patients: 9297 patients ≥55 yr (mean age 66 yr, 73% men) who had evidence of vascular disease or DM plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure.
Intervention: Ramipril 10 mg PO once daily vs. matching placebo.
Main Outcomes: Stroke, MI, or death from cardiovascular causes.
Results:

Outcome	RRR (95%CI)	NNT (CI)
Stroke	32% (16-44)	67 (43-145)
MI, stroke, or CV mortality	26 (19-43)	22% (14-30)
All-cause mortality	16% (5-25)	56 (32-195)

Treatment with ramipril reduced the risk of stroke (3.4% vs. 4.9%; RR 0.68; P<0.001).
Conclusions: In adults at high-risk for cardiovascular events, ramipril reduced the risk of stroke, as well as other vascular events and overall mortality. In addition, ACEI reduce risk of stroke beyond their hypertensive effect.

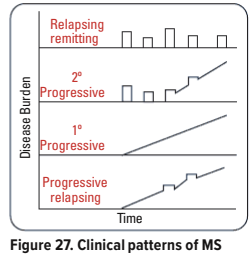


Figure 27. Clinical patterns of MS

Most symptoms in MS are due to cord, brainstem, and optic nerve lesions

Chronic Cerebrospinal Venous Insufficiency (CCSVI)
A theory proposed in 2008 described abnormal venous blood flow in patients with MS; while some RCTs are still underway, recent studies have largely discredited this highly controversial theory. That is, studies indicate no connection between CCSVI and MS

Clinical Patterns
- clinically isolated syndrome (CIS): first clinical episode that is suggestive of MS
- relapsing-remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- most RRMS goes on to become SPMS

Clinical Features
- an MS exacerbation is characterized by the onset of new neurological symptoms lasting more than 24 h, in the absence of fever or infection
  - symptoms typically peak over days to weeks, followed by variable improvement over weeks to months
  - in RRMS, average 0.4-0.6 relapses per yr, but higher disease activity in first yr of disease
- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. internuclear ophthalmoplegia), impaired gait, vertigo, bladder dysfunction, executive function impairment
- Lhermitte's sign: flexion of neck causes electric shock sensation down back into limbs suggestive of a dorsal cervical cord lesion
- Uhthoff's phenomenon: worsening of symptoms in heat
- SPMS: classically presents with progressive weakness and gait dysfunction with cerebellar findings of arms (i.e. intention tremor); associated features: fatigue, depression, subtle cognitive dysfunction, autonomic dysfunction

Diagnosis
- demonstration of both dissemination in time and space based on the revised McDonald criteria (2017)
  - dissemination in time: ≥2 attacks (lasting at least 24 h with 30 d between the 2 attacks), simultaneous presence of gadolinium enhancing and non-enhancing MRI lesions at any time, or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, presence of CSF oligoclonal bands
  - dissemination in space: ≥1 T2 lesions on MRI in at least 2 of the 4 CNS regions (periventricular, cortical/juxtacortical, infratentorial, or spinal cord) or developing a second attack that implicates a different CNS region

MS Variants
- Devic's = neuromyelitis optica (NMO): severe optic neuritis and longitudinally extensive transverse myelitis extending >3 vertebral segments (aquaporin-4 antibody positive)
- tumefactive MS: solitary lesion >2 cm mimicking neoplasms on MRI
- fulminant MS (Marburg): rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- pediatric MS: onset of MS before the age of 18
  - epidemiology: rare (1.35-2.5 in 100000 children)
  - presentation: more likely to present with isolated optic neuritis, isolated brainstem syndrome, or symptoms of encephalopathy compared to adults
  - course: 98% have RRMS
  - diagnosis and treatment similar to adult MS
  - differential diagnosis: in the setting of nonspecific CSF abnormalities and MRI evidence of white matter lesion, rule out acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, neuromyelitis optica, CNS malignancies, stroke, leukodystrophies, and mitochondrial disease
- ADEM: monophasic demyelinating disorder with multifocal neurologic symptoms with encephalopathy seen mainly in children, often following infection

Investigations
- MRI: demyelinating plaques appear as hyperintense lesions on T2-weighted MRI, with active lesions sometimes showing enhancement with gadolinium
  - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxtacortical region, and dorsolateral spinal cord
  - Dawson's fingers: periventricular lesions extending into corpus callosum
  - T1 "black holes"
  - cranial MRI is more sensitive than spinal MRI
- CSF: oligoclonal bands in 90%, increased IgG concentration
- evoked potentials (visual/auditory/somatosensory): delayed but well-preserved wave forms

Treatment
- acute exacerbation treatment: methylprednisolone 1000 mg IV daily x 3-7 d (no taper required) or prednisone 1000-1250 mg PO daily x 3-7 d (no taper required); if poor response to corticosteroids, may consider plasma exchange
- long-term treatment: vitamin D 4000 units daily
- disease modifying therapy (DMT)
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: teriflunomide, interferon-β (injection: Betaseron®, Avonex®, Rebif®), glatiramer acetate (injection: Copaxone®), dimethyl fumarate (Tecfidera®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion), fingolimod (Gilenya®), ocrelizumab (Ocrevus®), alemtuzumab (Lemtrada®), cladribine (Mavenclad®), ofatumumab (Kesimpta®)
  - increased risk of progressive multifocal leukoencephalopathy associated with natalizumab; also described with fingolimod, dimethyl fumarate, and ocrelizumab, but to a lesser degree

The Expanded Disability Status Scale (EDSS) is used as a measure of disability progression and is scored from 0 to 10 based on the neurologic exam and ambulation

Fingolimod for Relapsing-Remitting Multiple Sclerosis
Cochrane DB Syst Rev 2016;4:CD009371
Purpose: Systematic literature review of the evidence for fingolimod in treatment of relapsing-remitting MS.
Study: Meta-analysis of six RCTs (n=55152) investigating the benefits and harms of fingolimod and other disease modifying drugs in the treatment of relapsing-remitting MS.
Results: Compared to placebo and interferon β-1a, fingolimod increases the probability of being relapse free at 24 mo (RR 1.44 vs. placebo, RR 1.18 vs. interferon β-1a) but has little to no effect on disability progression (RR 1.07 vs. placebo, RR 1.02 vs. interferon β-1a). Fingolimod use was associated with a higher incidence of adverse events and discontinuation within 6 mo.
Conclusions: Fingolimod significantly reduces disease activity in relapse-remitting MS compared to placebo but does not prevent disability. Its use is associated with adverse events and requires close patient monitoring, particularly within the first 6 mo. Further study is needed to assess the benefits of fingolimod vs. other disease modifying drugs.

Recombinant Interferon β or Glatiramer Acetate for Delaying Conversion of the First Demyelinating Event to Multiple Sclerosis
Cochrane DB Syst Rev 2008;2:CD005278
Study: Meta-analysis of RCTs investigating clinically isolated syndrome (CIS) pateints treated with immunomodulatory drugs.
Primary Outcomes: Proportion of patients converting to clinically definite MS and adverse effects.
Results: Three trials (n=1160) tested the efficacy of interferon beta (IFN) and no trial tested glatiramer acetate (GA). The pooled odds ratio (OR) for patients on IFN vs. placebo at 1 yr was 0.53 (95% CI 0.40-0.71, P<0.0001). The 2 yr follow-up OR was 0.52 (95% CI 0.38-0.70, P<0.0001). There was no significant increase in adverse events for those on IFN.
Conclusions: IFN treatment can delay progression to clinically definite MS in patients with CIS over 2 yr.

See Landmark Neurology Trials for more information on the PreCISe trial. It details the efficacy of early treatment with glatiramer acetate in delaying onset of clinically definite multiple sclerosis (MS).

  - CIS: early treatment may delay potential second attack; glatiramer acetate, interferons, and teriflunomide all with RCT data
  - RRMS: first-line DMT reduces rate of relapse by about 30%; second-line by 50-90%
  - PPMS: ocrelizumab infusion (ORATORIO trial 2017)
  - SPMS: siponimod (Mayzent®)
- symptomatic treatment
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin, mirabegron
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantadine, modafinil, methylphenidate
  - depression: psychotherapy, antidepressants, lithium
  - constipation: high fibre intake, stool softener, laxatives
  - sexual dysfunction: sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®)
- education and counselling: MS Society, support groups, psychosocial issues

Prognosis

- good prognostic indicators: female, age <40 at onset, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease, good recovery between exacerbations
- PPMS: poor prognosis, higher rates of disability, poor response to therapy

Common Medications

Table 26. Common Medications for Neurological Disorders

Indications	Mechanism of Action/Class	Generic Name	Trade Name	Dosing	Contraindications	Side Effects
Parkinson's Disease	Dopamine precursor	levodopa + carbidopa	Sinemet®	Carbidopa 25 mg/levodopa 100 mg PO TID Maximum 200 mg carbidopa and 2000 mg levodopa/d	Use of MAO inhibitor in last 14 d	Nausea, hypotension, hallucinations, dyskinesias
	Dopamine agonist	pramipexole ropinirole rotigotine	Mirpaex® Requip® Neupro®	Initial: 0.125 mg TID Maximum: 4.5 mg/d Initial: 0.25 mg TID Maximum: 8 mg	Hypersensitivity	Hallucinations, nausea, dizziness, headache, insomnia, somnolence, application site reactions (rotigotine)
	MAOB inhibitor	rasagiline selegiline safinamide	Azilect® Eldepryl®	5 mg PO BID 1 mg PO once daily	Concomitant use of meperidine or tricyclic antidepressants	Headache, insomnia, dizziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinesia, risk of hypertensive crisis with tyramine-containing foods
Myasthenia Gravis	Acetylcholinesterase inhibitor	pyridostigmine	Mestinon®	600 mg/d PO divided in 5-6 doses Range 60-1500 mg/d	GI or GU obstruction	N/V, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness, bradycardia
Acute Migraine	Triptan (selective 5-hydroxytryptamine receptor agonist)	sumatriptan	Imitrex®	25-100 mg PO PRN, maximum 200 mg/d	Hemiplegic/basilar migraine, ischemic heart disease, CVD, uncontrolled HTN, use of ergotamine/5-HT1 agonist in past 24 h, use of MAO inhibitor in last 14 d, severe hepatic disease	Vertigo, chest pain, flushing, sensation of heat, hypertensive crisis, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, nausea, vomiting, headache, hyposalivation, fatigue
	Ergot (5-HT1D receptor agonist)	dihydroergotamine	Migranal®	Nasal spray 0.5 mg/spray, maximum 4 sprays/d	Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled HTN, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction, use of triptans in last 24 h, use of MAO inhibitors in last 14 d	Coronary artery vasospasm, transient myocardial ischemia, MI, ventricular tachycardia, ventricular fibrillation; may cause significant rebound headache
Migraine Prophylaxis	Anticonvulsant	topiramate	Topamax®	25 mg PO (in evening); may increase weekly by 25 mg/d to a max 50 mg BID	Nephrolithiasis	Sedation, mood disturbance, cognitive dysfunction, anorexia, nausea, diarrhea, paresthesias, metabolic acidosis, glaucoma, Stevens-Johnson syndrome, toxic epidermal necroylysis
	β-blocker	propranolol	Inderal®	80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q6-8 h	Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma	Fatigue, cognitive dysfunction, disturbed sleep, rashes, dyspepsia, dry eyes, heart failure, bronchospasm, risk of acute tachycardia and HTN if withdrawal

SJS: Stevens-Johnson Syndrome, TES: toxic epidermal necrolysis

Table 26. Common Medications for Neurological Disorders

Indications	Mechanism of Action/Class	Generic Name	Trade Name	Dosing	Contraindications	Side Effects
Epilepsy	Anticonvulsant for partial ± 2° generalization, generalized tonic-clonic	carbamazepine	Tegretol®	Start at 100-200 mg PO once daily to TID, increase by 200 mg/d up to 800-1200 mg/d	History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d	Drowsiness, headache, unsteadiness, dizziness, N/V, skin rash, agranulocytosis/aplastic anemia (rare)
	Anticonvulsant for partial, tonic-clonic, status epilepticus	phenytoin	Dilantin®	100 mg PO TID, maintenance dose up to 200 mg PO TID SE: 10-15 mg/kg IV loading dose then maintenance doses of 100 mg PO or IV q6-8 h	Hypersensitivity, pregnancy, breastfeeding; caution with P-450 interactions	Hypotension, Stevens-Johnson syndrome, toxic epidermal necroylysis, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, headache,, blood dyscrasias, nystagmus, N/V, constipation, sedation, teratogenic
	Anticonvulsant for partial or generalized, absence seizures	valproic acid	Depakene® Apo-Valproic®	10-15 mg/kg/d PO in divided doses, increase incrementally until therapeutic dose to max of 60 mg/kg/d	Hypersensitivity, hepatic disease, urea cycle disorders	Hepatic failure, headache, somnolence, alopecia, N/V, diarrhea, tremor, diplopia, thrombocytopenia, hypothermia, pancreatitis, encephalopathy, most teratogenic AED (dose-dependent)
	Anticonvulsant for absence seizures	ethosuximide	Zarontin®	500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses	Hypersensitivity (succinimides)	CNS depression, blood dyscrasias, SLE, Stevens-Johnson syndrome, GI symptoms
Stroke Prevention in Atrial Fibrillation	Anticoagulant (direct thrombin inhibitor)	dabigatran	Pradaxa®	110 mg PO BID or 150 mg PO BID	CrCl <30 mL/min, significant hemostatic impairment, or CNS lesions within 6 mo with high-risk of bleeding	Dyspepsia, gastritis, bleeding
	Anticoagulant (Factor Xa inhibitor)	rivaroxaban	Xarelto®	15 mg PO once daily or 20 mg PO once daily	Concomitant anticoagulant, hepatic disease, pregnancy, strong CYP3A4 and P-glycoprotein inhibitors e.g. itraconazole, ritonavir	Bleeding
	Anticoagulant (Factor Xa inhibitor)	apixaban	Eliquis®	2.5 mg PO BID or 5 mg PO BID	Active bleeding, gastrointestinal bleeding, recent cerebral infarction, active peptic ulcer disease with recent bleeding, hepatic disease with coagulopathy	Bleeding (conjunctival, gastrointestinal, gingival, contusion, hematoma, epistaxis, hematuria)
	Anticoagulant (Factor Xa inhibitor)	edoxaban	Savaysa®	30 mg PO or 60 mg PO once daily	Active bleeding, hepatic disease, CrCl <30 mL/min	Bleeding
Mild to Moderate Alzheimer's Disease or Dementia with Lewy Bodies	Cholinesterase Inhibitor	donepezil	Aricept®	5 mg PO once daily, may increase to 10 mg PO once daily after 4-6 wk	Hypersensitivity to donepezil or to piperidine derivatives	Diarrhea, N/V, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block
Multiple Sclerosis	MS Disease Modifying Therapy	interferon-β-1b interferon-β-1a SC interferon-β-1a IM	Betaseron® Rebif® Avonex®	0.25 mg (8 MU) SC every other day 44 µg SC 3 times/wk 30 µg IM once weekly	Pregnancy, hypersensitivity to natural or recombinant interferon-β	Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time)
	MS Disease Modifying Therapy	glatiramer acetate	Copaxone®	20 mg SC once daily	Hypersensitivity to glatiramer or mannitol	Injection site reactions, nausea, transient chest pain, vasodilation
	MS Disease Modifying Therapy	natalizumab	Tysabri®	300 mg IV given over 1 h, every 4 wk	Hypersensitivity to natalizumab, progressive multifocal leukoencephalopathy	Rash, nausea, arthralgia, headache, infections, rare risk of progressive multifocal leukoencephalopathy and melanoma
	MS Disease Modifying Therapy	fingolimod	Gilenya®	0.5 mg PO once daily	Not available	Diarrhea, transaminitis, headache, bradyarrhythmia, lymphopenia
Spasticity (i.e. MS)	Muscle Relaxant – Antispastic	baclofen	Lioresal®	5 mg PO TID, increase by 15 mg/d q3d to max dose 80 mg/d in three divided doses	Hypersensitivity to baclofen	Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea

SJS: Stevens-Johnson Syndrome, TES: toxic epidermal necrolysis

Landmark Neurology Trials

Trial Name	Reference	Clinical Trial Details
Stroke		
NASCET	NEJM 1991;7:445-53	**Title**: Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High-Grade Carotid Stenosis **Purpose**: To assess the efficacy of carotid endarterectomy for reducing stroke risk in patients with a recent adverse cerebrovascular event and ipsilateral carotid stenosis. **Methods**: 659 patients with recent (≤120d) hemispheric or retinal TIA or nondisabling stroke with 70-99% stenosis received optimal medical care. Those assigned to surgical treatment underwent carotid endarterectomy. **Results**: Estimated cumulative risk of any ipsilateral stroke at 2yr was 26% in medical patients and 9% in surgical patients (AR reduction, 17%; P<0.001), and 13.1% and 2.5%, respectively, for major or fatal ipsilateral stroke (10.6%; P<0.001). **Conclusion**: Carotid endarterectomy effectively reduces stroke risk in patients with a recent adverse cerebrovascular event and ipsilateral carotid stenosis.
NINDS tPA	NEJM 1995;333:1581-87	**Title**: Tissue Plasminogen Activator for Acute Ischemic Stroke **Purpose**: To investigate the clinical efficacy of IV tPA in acute ischemic stroke. **Methods**: Patients with acute ischemic stroke randomly assigned to receive tPA or placebo. **Results**: At 24h, there was no significant differences in neurologic improvement between tPA and placebo. Clinical benefit of tPA was observed at 3 mo for all outcome measures. Patients treated with rtPA were 30% less likely to be disabled at 3mo. tPA was associated with significantly more symptomatic intracerebral hemorrhage within 36 h after stroke. **Conclusion**: When administered within 3 h of ischemic stroke, tPA improved clinical outcomes despite a greater risk of symptomatic intracerebral hemorrhage.
WASID	NEJM 2005;352:1305-16	**Title**: Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis **Purpose**: To compare the safety and efficacy of warfarin and aspirin in the treatment of stroke caused by atherosclerotic intracranial arterial stenosis. **Methods**: 569 patients with TIA or stroke caused by 50-99% stenosis were randomized to receive warfarin (target international normalized ratio, 2.0-3.0) or aspirin (1300 mg once daily). **Results**: Study stopped early due to safety concerns. Adverse events included death (4.3% on aspirin vs. 9.7% on warfarin; P=0.02), major hemorrhage (3.2% vs. 8.3%; P=0.01), and MI or sudden death (2.9% vs. 7.3%; P=0.02) during 1.8 yr mean follow-up. **Discussion**: In patients with intracranial arterial stenosis, warfarin afforded no clinical benefit and was associated with more adverse events. Aspirin is thus preferable.
SPARCL	NEJM 2006;355:549-59	**Title**: High-Dose Atorvastatin after Stroke or Transient Ischemic Attack **Purpose**: To investigate whether statins reduce the risk of stroke after a recent stroke or TIA. **Method**: 4731 patients with stroke or TIA within 1-6 mo and LDL=2.6-4.9 mmol/L and without coronary disease were randomly assigned to receive 80 mg atorvastatin daily or placebo. **Results**: Fatal or nonfatal stroke occured in 11.2% of patients receiving atorvastatin and 13.1% receiving placebo (5-yr absolute reduction in risk, 2.2%; adjusted hazard ratio, 0.84; 95% CI, 0.71 to 0.99; P=0.03). The atorvastatin group experienced relatively more hemorrhagic strokes (hazard ratio 1.66 (1.08-2.55)). **Conclusion**: Atorvastatin reduced the overall incidence of strokes in patients with recent stroke or TIA, despite an increase in rates of hemorrhagic stroke
ECASS 3	NEJM 2008;359:1317-29	**Title**: Thrombolysis With Alteplase 3 to 4.5 Hours After Acute Ischemic Stroke **Purpose**: To investigate the efficacy and safety of alteplase administered 3-4.5 h following stroke onset. **Methods**: Randomly assigned 821 patients with acute ischemic stroke to receive IV alteplase (0.9 mg/kg) or placebo. Primary outcome was disability at 90d (favorable outcome: 0-1 on modified Rankin scale) or unfavorable outcome (2-6). **Results**: Alteplase was associated with more favourable outcomes than placebo (52.4% vs. 45.2%; OR, 1.34; 95% CI, 1.02-1.76; P=0.04). Intracranial hemorrhage was more frequent on alteplase vs. placebo (27.0% vs. 17.6%; P=0.001). No significant difference in mortality or adverse events. **Conclusion**: In patients with acute ischemic stroke, IV alteplase administered 3-4.5 h after symptom onset significantly improved clinical outcomes but also increased the frequency of ICH.
RELY	NEJM 2009;361:1139-51	**Title**: Dabigatran Versus Warfarin in Patients with Atrial Fibrillation **Purpose**: To investigate the efficacy and safety of dabigatran vs. warfarin in preventing stroke or systemic embolism in patients with AFib. **Methods**: 18,113 patients with AFib and risk of stroke were randomly assigned to receive dabigatran 110-150 mg BID or adjusted-dose warfarin. **Results**: Rates of stroke or systemic embolism were 1.69%/yr on warfarin and 1.53%/yr on 110 mg dabigatran (relative risk with dabigatran, 0.91; 95% CI, 0.74-1.11) and 1.11%/yr on 150 mg dabigatran (0.66 (0.53-0.82)). Frequency of major bleeding was 3.36%/yr on warfarin and 2.71%/yr on 110 mg of dabigatran (P=0.003) and 3.11%/yr on 150 mg dabigatran (P=0.31). **Conclusion**: When compared to warfarin, dabigatran has potential to lower stroke rates or major hemorrhage depending on dose.
CREST	NEJM 2010;363:11-23	**Title**: Stenting Versus Endarterectomy for Treatment of Carotid-Artery Stenosis **Purpose**: To investigate the efficacy and safety of carotid-artery stenting vs. carotid endarterectomy for treating carotid-artery stenosis. **Methods**: 2502 patients with carotid stenosis were randomly assigned to carotid-artery stenting or carotid endarterectomy. Primary composite outcome was MI, stroke, or death from any cause or any ipsilateral stroke within 4yr. **Results**: Estimated 4-year rates of the primary outcome did not significantly differ between stenting and endarterectomy (7.2% vs. 6.8%; hazard ratio with stenting, 1.11 (0.81-1.5)); P=0.51). Rates of individual endpoint components for stenting vs. endarterectomy were 0.7% vs. 0.3%, P=0.18 for death; 4.1% vs. 2.3%, P=0.01 for stroke; and 1.1% vs. 2.3%, P=0.03 for MI. **Conclusion**: Composite primary outcome risk did not differ significantly between stenting and endarterectomy in patients with carotid stenosis.
ARISTOTLE	NEJM 2011;365:981-92	**Title**: Apixaban Versus Warfarin in Patients With Atrial Fibrillation **Purpose**: To assess the efficacy of apixaban in reducing the risk of stroke as compared to warfarin. **Methods**: 18,201 patients with AFib and one additional risk factor for stroke were randomized to receive either apixaban or warfarin. The primary outcome was stroke or systemic embolism. **Results**: The rate of stroke or systemic embolism was lower in the apixaban group than in the warfarin group (1.27% vs. 1.60%; P<0.001 for noninferiority, P=0.01 for superiority). The rates of major bleeding (2.13% vs. 3.09%; P<0.001) and death (3.52% vs. 3.94%; P=0.047) were lower in the apixaban group than in the warfarin group. **Conclusion**: In patients with AFib, apixaban was superior to warfarin for preventing stroke or systemic embolism with lower rates of major bleeding and death.
AVERROES	NEJM 2011;364:806-17	**Title**: Apixaban in Patients with Atrial Fibrillation **Purpose**: To investigate the efficacy and safety of apixaban in preventing stroke in patients with AFib. **Methods**: 5599 patients with AFib at increased risk for stroke and who were unsuitable for vitamin K antagonist therapy were randomly assigned to receive 5 mg apixaban BID or aspirin (81-324 mg daily). **Results**: Study terminated early due to clear apixaban benefit. Rates of stroke or systemic embolism were 1.6%/yr on apixaban and 3.7%/yr on aspirin (hazard ratio with apixaban, 0.45 (0.32 to 0.62); P<0.001). There were no significant differences in rates of major bleeding or intracranial bleeding. **Conclusion**: Apixaban reduced the risk of stroke or systemic embolism without increasing bleeding or hemorrhage risk in patients with AFib unsuitable for vitamin K antagonists.
ROCKET AF	NEJM 2011;365:883-91	**Title**: Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation **Purpose**: To investigate if rivaroxaban is noninferior to warfarin in preventing stroke or systemic embolism in AFib. **Methods**: 14264 patients with nonvalvular AFib at increased risk for stroke were randomly assigned to receive either rivaroxaban (20 mg once daily) or dose-adjusted warfarin. **Results**: Rates of stroke or systemic embolism were 1.7%/yr on rivaroxaban and 2.2%/yr on warfarin (hazard ratio, 0.79 (0.66 to 0.96); P<0.001 for noninferiority). Significant reductions in ICH (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) were seen in the rivaroxaban group. **Conclusion**: Rivaroxaban was noninferior to warfarin in patients with AFib for preventing stroke or systemic embolism with lower risks of ICH and fatal bleeding.
SAMMPRIS	NEJM 2011;365:993-1003	**Title**: Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis **Purpose**: To compare the efficacy of percutaneous transluminal angioplasty and stenting (PTAS) vs. medical management in intracranial arterial stenosis. **Methods**: 451 patients with recent TIA or stroke attributed to 70-99% stenosis were randomly assigned to aggressive medical management plus PTAS or aggressive medical management alone. **Results**: 30 d stroke or death rate was 14.7% and 5.8% in the PTAS and medical-management group, respectively (P=0.002). 1-yr rates of the primary end point (stroke or death within 30 d or after a revascularization during follow-up or stroke in the territory of the qualifying artery beyond 30d) were 20.0% in PTAS and 12.2% in medical-management (P=0.009). **Conclusion**: Aggressive medical management in patients with intracranial arterial stenosis was superior to PTAS.

Trial Name	Reference	Clinical Trial Details
INTERACT2	NEJM 2013;368:2355-65	**Title**: Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage **Purpose**: To investigate the efficacy of rapid lowering of elevated BP for improving outcomes in patients with intracerebral hemorrhage. **Methods**: 2839 patients with spontaneous intracerebral hemorrhage and elevated sBP were randomly assigned to receive intensive treatment (target sBP <140 mmHg within 1 hr) or guideline-based treatment (target sBP <180 mm Hg Hg). **Results**: 52.0% receiving intensive treatment vs. 55.6% receiving guideline-based treatment experienced a primary outcome event (death or major disability) (OR, 0.87 (0.75-1.01); P=0.06). Intensive treatment was associated with significantly lower modified Rankin scores (OR for greater disability, 0.87 (0.77-1.00); P=0.04). **Conclusion**: Intensive BP lowering in intracerebral hemorrhage did not significantly reduce rates of death or severe disability but may improve functional outcomes.
ESCAPE	NEJM 2015;3721019-30	**Title**: Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke **Purpose**: To investigate rapid endovascular treatment plus standard care in acute ischemic stroke with a proximal intracranial arterial occlusion, small infarct core, and moderate-good collateral circulation. **Methods**: 316 patients randomly assigned to receive endovascular treatment with the use of available thrombectomy devices plus standard of care (intervention group) or standard care alone (control group). **Results**: The intervention reduced mortality (10.4%, vs. 19.0% in controls; P=0.04) and was associated with improved scores on the modified Rankin scale at 90 d (common OR, 2.6; 95% CI, 1.7 to 3.8; P<0.001). **Conclusion**: Rapid endovascular treatment improved functional outcomes and reduced mortality in select patients with acute ischemic stroke.
MR CLEAN	NEJM 2015;372:11-20	**Title**: A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke **Purpose**: To investigate functional outcomes of intraarterial treatment for emergency revascularization in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion. **Methods**: 500 patients that could be treated intraarterially within 6h after symptom onset were randomly assigned to either intraarterial treatment plus standard care or standard care alone. **Results**: The rate of functional independence (modified Rankin score, 0 to 2) was higher in the intervention group (32.6% vs. 19.1%; absolute difference, 13.5%, 95% CI, 5.9 to 21.2). Rates of mortality or symptomatic intracerebral hemorrhage were not significantly different between groups. **Conclusion**: Intraarterial treatment within 6 h following stroke onset was safe and effective in acute ischemic stroke caused by intracranial, proximal arterial occlusion of the anterior circulation.
DAWN	NEJM 2018;378:11-21	**Title**: Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct **Purpose**: To investigate the efficacy and safety of endovascular thrombectomy performed >6 h following ischemic stroke onset. **Methods**: 206 patients with acute stroke who were well 6-24 h earlier with mismatch between clinical deficit and infarct were randomly assigned to thrombectomy plus standard care or standard care alone (control). **Results**: At 90 d, mean scores on a modified Rankin scale were 5.5 in thrombectomy and 3.4 in controls (adjusted difference, 2.0 points (1.1-3.0); posterior probability of superiority, >0.999), and the rate of functional independence were 49% and 13%, respectively (adjusted difference, 33% (24-44); posterior probability of superiority, >0.999). **Conclusion**: Adding thrombectomy to standard of care improved disability outcomes in patients with acute stroke who were well 6-24 h earlier with clinical deficit and infarct mismatch.
POINT	NEJM 18;379:215-25	**Title**: Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA **Purpose**: To investigate the efficacy of clopidogrel plus aspirin to reduce the rate of stroke recurrence during the first 3 mo following a minor ischemic stroke or TIA. **Methods**: 4881 patients with minor ischemic stroke or high-risk TIA were randomly assigned to clopidogrel plus aspirin or aspirin plus placebo. **Results**: Fewer major ischemic events were observed in those receiving clopidogrel plus aspirin (5%) vs. aspirin plus placebo (6.5%) (hazard ratio, 0.75 (0.59-0.95); P=0.02). Risk of major hemorrhage was greater in those receiving clopidogrel plus aspirin (0.9%) vs. those receiving aspirin plus placebo (0.4%) (2.32 (1.10-4.87); P=0.02). **Conclusion**: Clopidogrel plus aspirin lowers risk of major ischemic events but increases risk of major hemorrhage in patients with minor ischemic stroke or high-risk TIA.
Multiple Sclerosis		
Interferon-β-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical **results** of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. 1993	Neurology 1993;43:655-61	**Title**: Interferon-β-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicentre, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group **Purpose**: To investigate the efficacy of Interferon-β-1b (IFNB) in relapsing-remitting MS. **Methods**: 372 ambulatory patients with relapsing-remitting MS self-administered either placebo, 1.6 million international units (MIU) of IFNB, or 8 MIU of IFNB. **Results**: After 2 yr, rates of annual clinical exacerbation for patients on placebo were 1.27; 1.17 for 1.6 MIU IFNB; and 0.84 for 8 MIU IFNB, indicating both treatment groups performed significantly better than placebo. In the 8 MIU group, there was a twofold reduction in the frequency of moderate-severe attacks. **Conclusion**: Interferon-β-1b reduces relapse rate and severity of relapses in relapsing-remitting MS.
PreCISe	Lancet 2009;374:1503-11	**Title**: Effect of Glatiramer Acetate on Conversion to Clinically Definite Multiple Sclerosis in Patients with Clinically Isolated Syndrome (Precise Study): A Randomised, Double-Blind, Placebo-Controlled Trial **Purpose**: To assess the efficacy of early treatment with glatiramer acetate in delaying onset of clinically definite MS. **Methods**: 481 patients with clinically isolated syndrome with unifocal manifestation, and ≥2 T2-weighted brain lesions >6 mm, received SC glatiramer acetate (20 mg/d) or placebo for up to 36 mo. **Results**: Relative to placebo, the risk of developing clinically definite MS was reduced by 45% with glatiramer acetate (hazard ratio 0.55, 95% CI 0.40-0.77; P=0.0005). It prolonged the time for 25% of patients to convert to clinically definite disease by 115%. Injection-site reactions and immediate post-injection reactions were the most common adverse events. **Conclusion**: In patients presenting with clinically isolated syndrome and brain lesions, conversion to clinically definite MS can be delayed by early treatment with glatiramer acetate.
Seizure Disorders and Epilepsy		
MESS	Lancet 2005;365:2007-13	**Title**: Immediate Versus Deferred Antiepileptic Drug Treatment for Early Epilepsy and Single Seizures: A Randomised Controlled Trial **Purpose**: To investigate the relative benefits and risks of initiating or withholding antiepileptic drug treatment in patients with few or infrequent seizures. **Methods**: 1443 patients with single seizures or early epilepsy were randomly assigned to receive either immediate or deferred antiepileptic drug treatment. **Results**: Immediate treatment prolonged time to 1st seizure (hazard ratio 1.4; (95% CI 1.2-1.7)), 2nd seizure (1.3 (1.1-1.6)), and first tonic-clonic seizure (1.5 (1.2-1.8)). Time to 2-yr remission of seizures was reduced by immediate treatment (P=0.023). The proportion of patients that were seizure-free between years 3-5 were 76% on immediate treatment and 77% on deferred treatment. **Conclusion**: In individuals with single or infrequent seizures, seizure occurrence in the first 1-2 yr is reduced by immediate antiepileptic drug treatment, but long-term remission is not affected.
SANAD	Lancet 2007;369:1016-26	**Title**: The SANAD Study of Effectiveness of Valproate, Lamotrigine, or Topiramate for Generalised and Unclassifiable Epilepsy: An Unblinded Randomised Controlled Trial **Purpose**: To investigate the long-term effects of valproate, lamotrigine, and topiramate in patients with generalized onset seizures or seizures that are not easily classified. **Methods**: Between 1999-2004 during the initial trial, patients were randomly assigned to receive valproate, lamotrigine, or topiramate, and follow-up data were obtained up to 2006. **Results**: Valproate was significantly better than topiramate for time to treatment failure (hazard ratio 1.57 (95% CI 1.19-2.08)), and significantly better than lamotrigine for time to 12-mo remission (0.76 (0.62-0.94)). **Conclusion**: Valproate should remain the first line therapy for generalised and unclassified epilepsies due to superior efficacy and safety profiles.

Trial Name	Reference	Clinical Trial Details
Alzheimer's Disorder		
CATIE-AD	Am J Psychiatry 2011;168:831-839	**Title:** Cognitive Effects of Atypical Antipsychotic Medications in Patients with Alzheimer's Disease: Outcomes from CATIE-AD **Purpose:** To examine the effects of time and treatment on neuropsychological functioning during the Clinical Antipsychotic Trials of the Intervention Effectiveness-Alzheimer's Disease study. **Methods:** 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behaviour were randomized to receive olanzapine, quetiapine, risperidone, or placebo in a multicentre double-blinded RCT. MMSE and Alzheimer's Disease Assessment Scale (ADAS) scores were measured at 36 wk. **Results:** Patients receiving atypical antipsychotics exhibited a faster rate of cognitive decline as measured by MMSE scores (– 0.067/wk vs. -0.007/ wk). They also had a significantly faster decline compared to placebo on a composite measure of ADAS, MMSE, and various other cognitive tests (-0.011/wk vs. -0.001/wk). **Conclusions:** Long-term use of atypical antipsychotics for behavioural symptoms and psychosis in dementia patients is associated with greater rates of cognitive decline.
Neuropathic Pain		
A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. Oxman et al. 2005	NEJM 2005;352:2271-84	**Title:** A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults **Purpose:** To investigate whether vaccination against herpes zoster would decrease the incidence and/or severity of infection or postherpetic neuralgia in older adults. **Methods:** 38546 adults aged ≥60 yr were randomized to receive live attenuated Oka/Merck VZV vaccine (zoster vaccine) or placebo. **Results:** Vaccination reduced herpes zoster illness burden by 61.1% (P<0.001), incidence of infection by 51.3% (P<0.001), and incidence of PHN by 66.5% (P<0.001). **Conclusion:** Among older adults, the zoster vaccine significantly reduced morbidity from herpes zoster and postherpetic neuralgia.

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NS Neurosurgery

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Acronyms

AVF	arteriovenous fistula	H/A	headache	NPH	normal pressure hydrocephalus	SPECT	single photon emission computed tomography
AVM	arteriovenous malformation	IC	internal capsule	OPLL	ossification of posterior longitudinal ligament	SRS	stereotactic radiosurgery
BBB	blood-brain barrier	ICA	internal carotid artery	PAG	periaqueductal grey matter	STN	subthalamic nucleus
C&S	culture and sensitivity	ICF	intracellular fluid	PCom	posterior communicating artery	TBI	traumatic brain injury
CBF	cerebral blood flow	ICH	intracerebral hemorrhage	PET	positron emission tomography	UMN	upper motor neuron
CN	cranial nerve	IVH	intraventricular hemorrhage	PLL	posterior longitudinal ligament	VPL	ventral posterolateral
CNS	central nervous system	LMN	lower motor neuron	PNET	primitive neuroectodermal tumour	VPM	ventral posteromedial
CPA	cerebellopontine angle	LOC	level of consciousness	PVG	periventricular grey matter	WBRT	whole brain radiation therapy
CPP	cerebral perfusion pressure	LP	lumbar puncture	SAH	subarachnoid hemorrhage	XRT	radiotherapy
CVR	cerebral vascular resistance	MAP	mean arterial pressure	SCI	spinal cord injury		
DBS	deep brain stimulation	MLS	midline shift	SDH	subdural hematoma		
DI	diabetes insipidus	MRA	magnetic resonance angiography	SEEG	stereoelectroencephalography		
ECF	extracellular fluid	NC	neurogenic claudication	SIADH	syndrome of inappropriate antidiuretic hormone		
EVD	external ventricular drain	NCCT	non-contrast CT				
GCS	Glasgow coma scale	NICU	neonatal intensive care unit				
GPi	globus pallidus pars interna						

Basic Anatomy Review

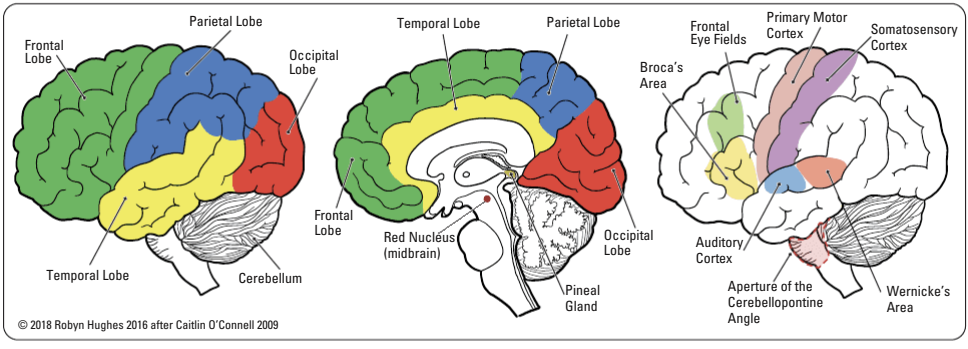

Figure 1. Basic surface anatomy

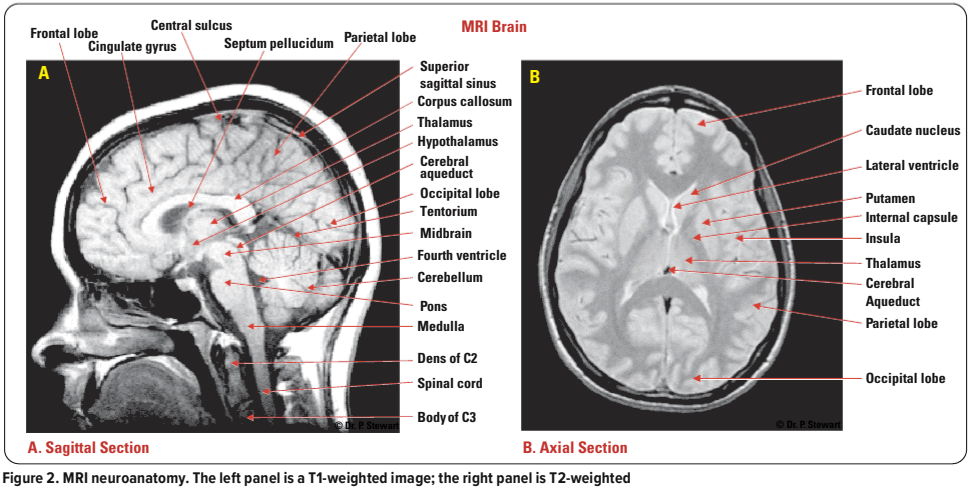

Figure 2. MRI neuroanatomy. The left panel is a T1-weighted image; the right panel is T2-weighted

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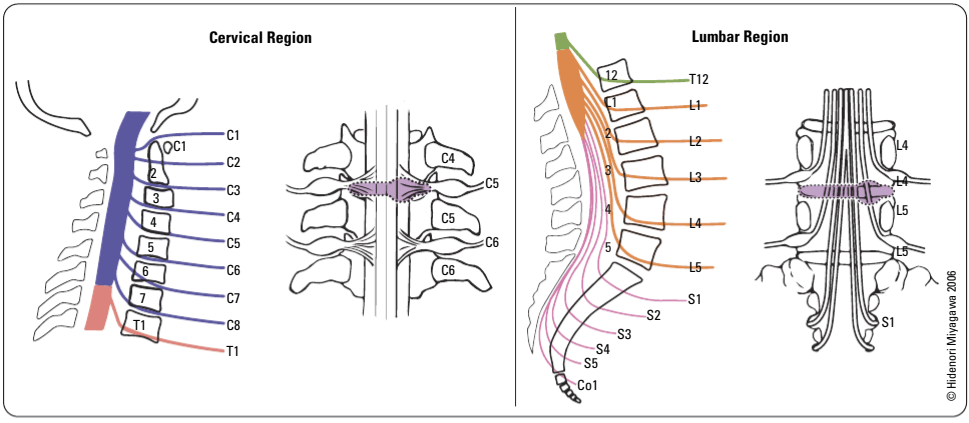

Figure 3. Relationship of nerve roots to vertebral level in the cervical and lumbar spine
Note: AP (anterior-posterior) views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement

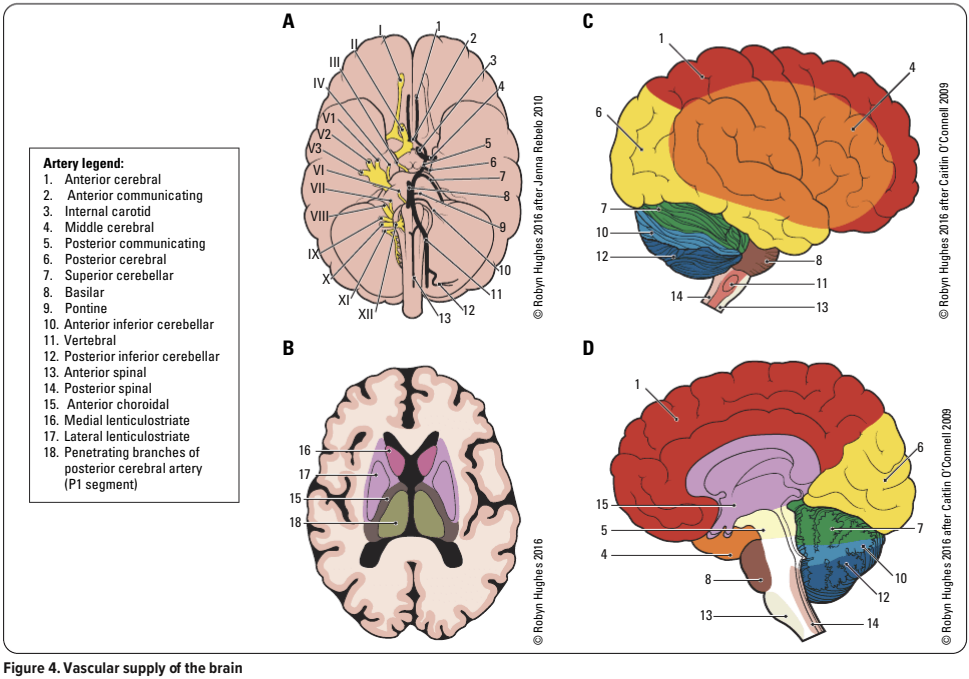

Figure 4. Vascular supply of the brain
Please see legend for artery names. 4A. Circle of Willis, most common variant. 4B. Vascular supply to subcortical structures, axial view. 4C. Vascular territories of the brain, sagittal view, seen laterally. 4D. Vascular territories of the brain, sagittal view, seen medially

Differential Diagnoses of Common Presentations

Table 1. Differential Diagnoses of Common Presentations

Intracranial Mass Lesions	Disorders of the Spine	Peripheral Nerve Lesions
Tumour Metastasis Glioma Meningioma Vestibular schwannoma (acoustic neuroma) Pituitary adenoma Primary CNS lymphoma **Pus/Inflammation** Cerebral abscess, extradural abscess, subdural empyema Encephalitis, e.g. Herpes Simplex Virus (see Infectious Diseases, ID18) Tumefactive multiple sclerosis (MS) Sarcoidosis **Blood** Extradural (epidural) hematoma SDH Ischemic stroke Hemorrhage: SAH, ICH, IVH **Cyst** Arachnoid cyst Dermoid cyst Epidermoid cyst Colloid cyst (3rd ventricle)	**Extradural** Degenerative: disc herniation, canal stenosis, spondylolisthesis/spondylolysis Infection/inflammation: osteomyelitis, discitis Ligamentous: OPLL Trauma: mechanical compression/instability, hematoma Tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma **Intradural Extramedullary** Vascular: dural AVF, SDH (especially if on anticoagulants) Tumours (40% of all spinal tumours): meningioma, schwannoma, neurofibroma **Intradural Intramedullary** Tumours (5% of all spinal tumours): gliomas, ependymomas, hemangioblastomas, and dermoids Syringomyelia: trauma, congenital, idiopathic Infectious/inflammatory: TB, sarcoid, transverse myelitis Vascular: AVM, ischemia	**Neuropathies** Traumatic Entrapments Iatrogenic Inflammatory Tumours

INTRACRANIAL PATHOLOGY

Intracranial Pressure Dynamics

Table 2. Approach to Intracranial Pathology

Issue	Time Frame	Features
Vascular	Sudden	No H/A = occlusive
		H/A = hemorrhagic
Metabolic	Hours to days	Affects entire CNS
Infectious	Days to weeks	Often a source of infection or immunodeficiency on history
Tumour	Months	Increased ICP:
		Initially → H/A
		Constant
		Progressive
		Severe
		Worse in morning and/or wakes from sleep
		As ICP increases:
		Blurry vision
		Projectile vomiting (may initially present without nausea)
		Severely raised ICP:
		Cushing's triad
		1. Bradycardia
		2. HTN
		3. Respiratory irregularity

Table 3. Consequences of Common Brain Lesions

Location of Lesion	Consequence
Frontal Lobe Usually large lesions produce symptoms	Abulia, disinhibition, apathy, executive dysfunction, deficits in orientation and judgment, ± primitive reflex re-emergence, ± contralateral UMN signs (upgoing Babinski reflex and pronator drift)
Frontal Eye Fields	Gaze deviation toward side of a destructive lesion Gaze deviation away from irritative lesion (i.e. seizure)
Broca's Area Posterior inferior frontal gyrus of dominant hemisphere	Non-fluent, dysarthric, aphasia Repetition impaired Comprehension spared
Occipital Lobe	Contralateral homonymous hemianopia
Parietal Lobe Either side Dominant side (left) Non-dominant side (right)	Dressing apraxia, cortical sensory loss, lower homonymous quadrantanopia Inattention or extinction of non-dominant side Aphasias, Gerstmann's syndrome Hemispatial neglect, apraxias, agnosias (if temporal involvement)
Temporal Lobe	Hippocampus: anterograde amnesia Upper homonymous hemianopia Wernicke's aphasia (if left/dominant side)
Wernicke's Area Posterior superior temporal gyrus of dominant hemisphere	Fluent aphasia Repetition impaired Comprehension impaired
Basal Ganglia	Resting tremor Chorea Athetosis Hemiplegia if IC involved
Subthalamic Nucleus	Contralateral hemiballismus
Brainstem	Absent brainstem reflexes: oculocephalic, oculovestibular, corneal, gag, and cough Dorsal midbrain/pineal gland: Parinaud's syndrome (supranuclear upward gaze palsy) Pons: locked-in syndrome Below red nucleus: decerebrate posture Above red nucleus: decorticate posture Reticular activating system (midbrain): reduced level of arousal CPA: disequilibrium, ataxia, and CN V, VII, VIII deficits
Cerebellar Hemisphere	Intention tremor Ipsilateral limb ataxia Fall towards side of lesion
Cerebellar Vermis	Truncal ataxia Dysarthria

ICP/Volume Relationship

- Monro-Kellie doctrine: the brain is encased in a rigid skull with constant intracranial volume
  - the intracranial space contains CSF, blood, and brain
- the increase in one constituent will: 1) necessitate the redistribution of CSF, blood, and/or brain; and 2) increase ICP
- compensatory mechanisms initially maintain a normal ICP
- compensatory reserve (spatial compensation): 60-80 mL in young people, 100-140 mL in elderly (largely due to cerebral atrophy)
  - immediate: egress of CSF through foramen magnum to spinal canal, displacement of venous blood from sinuses into jugular veins
- once compensation is exhausted, ICP rises exponentially:
  - late: displacement of arterial blood (decreased CPP) eventually leading to ischemia, increasing brain edema, or expanding mass displaces parenchyma into compartments under less pressure (see *Table 4, NS7*)
  - end: cessation of cerebral perfusion when ICP>MAP, cerebral herniation down into foramen magnum

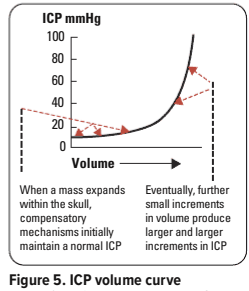

Figure 5. ICP volume curve
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Cerebral Blood Flow

- the brain receives about 15% of cardiac output (~750 mL/min)
- CBF is the vital parameter for brain function, it depends on CPP and CVR
- CPP is the difference between MAP and ICP (normal CPP >50 mmHg)
- cerebral autoregulation: mechanism that maintains constant CBF despite changes in CPP, unless:
  - high ICP such that CPP <40 mmHg
  - MAP >150 mmHg or MAP <50 mmHg (individuals with HTN may require a higher minimal MAP to avoid hypotension and complications associated with challenges in autoregulation)
  - increased CO_2 = increased CBF via vasodilation
  - O_2 <50 mmHg = increased CBF via vasodilation
  - brain injury: e.g. SAH, severe trauma

ICP Measurement

- normal ICP 10-15 mmHg for adult, 3-7 mmHg for child, 1.5-6 mmHg for infant; varies with patient position
- ICP >25 mmHg → end-organ damage possible, treatment should be initiated
- ICP >40 mmHg → life-threatening emergency, urgent pressure reduction required
  - ICP measurements should be considered in the context of underlying pathology when evaluating severity

Acute Monitoring

- indications include: severe TBI (GCS <8T) + abnormal CT; or severe TBI and normal CT if two or more of: age >40, BP <90 mmHg, or abnormal motor posturing; "T" for GCS<8T refers to presence of intubation, tracheostomy or other factors that might affect the ability to test verbal responses:
  - intraventricular catheter (EVD) is the "gold standard"; most accurate method and allows therapeutic drainage of CSF
  - parenchymal ICP monitor
  - non-invasive methods (e.g. transcranial Doppler, CT/MRI, fundoscopy, etc.) fail to measure ICP accurately enough to be used as routine measurement techniques
- Licox monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

Elevated ICP

Etiology

- **pathologic structure**
  - intracranial mass (tumour, cyst)
  - cerebral edema
    - vasogenic: BBB compromised (meningitis, hypertensive encephalopathy, tumour, late ischemia)
    - cytotoxic: BBB intact (cell death in: early ischemia, brain injury, encephalitis, status epilepticus)
    - interstitial: transudation of CSF into periventricular white matter in hydrocephalus (transependymal edema)
    - osmotic: osmotic gradient increases intracellular free H2O (acute hyponatremia, hepatic encephalopathy)
  - other space occupying lesions: depressed skull fracture, foreign body, pus/empyema
- **increased intracranial blood volume**
  - space occupying blood: epidural and subdural hematomas, intraparenchymal and subarachnoid hemorrhages
  - venous obstruction (venous sinus thrombosis, superior vena cava syndrome, cor pulmonale, venous sinus compression)
  - impaired autoregulation (hypotension, HTN, brain injury, status epilepticus)
  - vasodilation (increased pCO_2/decreased pO_2/decreased extracellular pH)
- **increased intracranial CSF volume** (see *Hydrocephalus, Table 7, NS9*)
  - non-obstructive: increased production (rare, choroid plexus papilloma, secretory vestibular schwannoma), decreased absorption (e.g. post-traumatic, post-SAH/IVH, post-meningitis)
  - obstructive: blockage in CSF pathway
- **idiopathic intracranial HTN** (pseudotumour cerebri; see *Idiopathic Intracranial Hypertension, NS8*)

CBF = CPP / CVR
CPP = MAP – ICP

MAP Targets in Trauma
TBI: MAP >80 mmHg
SCI: MAP between 85-90 mmHg in first 7 d post injury

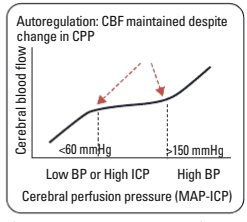

Figure 6. Cerebral autoregulation curve
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Serial LP can be used for ICP monitoring, although it is not the most accurate. LP can precipitate tonsillar and uncal herniation with elevated ICP. This procedure is absolutely contraindicated in the setting of suspected acutely raised ICP or obstructive hydrocephalus, and relatively contraindicated with known/suspected intracranial mass

Consider Monitoring ICP in the Following Situations
- Patients with an abnormal head CT (SAH, hematoma, contusion, basal cistern compression, swelling, and herniation), and GCS score ≤8 after CPR

OR
- Patients with a normal head CT and GCS score of ≤8 AND the presence of two or more of the following:
  - >40 yr
  - Unilateral or bilateral motor posturing
  - sBP <90 mmHg
  - Postoperative monitoring
  - Investigation of NPH

Cautioned Medication Use in Elevated ICP
- Nitroprusside: can raise ICP in patients with intracranial mass lesions due to direct vasodilation (arterial>venous)
- Nitroglycerine: can raise ICP via vasodilation but less so than nitroprusside because venous>arterial
- Succinylcholine: induced fasciculations may increase ICP

Clinical Features

Table 4. Clinical Features of Elevated ICP

Clinical Features	Acutely Elevated ICP	Chronic Progressive ICP Elevation
Headache	Both aggravated by stooping, coughing, and straining (Valsalva) Morning H/A: vasodilation due to increased CO_2 with recumbency	
N/V	Present in both, though greater predilection in acutely elevated ICP	
LOC	Lethargy if ICP = dBP or midbrain compression	Irritability, inattentiveness. Normal or modestly reduced LOC, confusion
GCS	Significant decline in GCS Best index to monitor progress and predict outcome of acute intracranial process (see *Neurotrauma, NS35*)	Can be unchanged or modestly decreased
Optic Disc Changes	Subtle changes suggesting papilledema (subtle elevations in disc margin, mild disc hyperemia) ± retinal hemorrhages (may take 24-48 h to develop)	Obvious papilledema
Visual Changes	Less common. Often not affected initially; however, visual obscurations, flickering, or blurring can occur	Optic atrophy/blindness due to chronic papilledema Enlarged blind spot, if advanced ➔ episodic constrictions of visual fields ("grey-outs" lasting ~20 min) Differentiate from papillitis (usually unilateral with decreased visual acuity)
Extraocular Movements	Less common. CN VI palsy: due to long intracranial course, more sensitive to ICP changes and thus earlier sign of acutely increased ICP Often falsely localizing (causative lesion remote to nerve) Upward gaze palsy and upward gaze impairment ("sunset eyes") (especially in children with obstructive hydrocephalus due to pressure on tectal plate)	Often full extraocular movement
Herniation Syndromes	Often occur	Present if acute-on-chronic presentation
Neurologic Deficits	Focal deficits present	Focal deficits can be present

Blood-Brain Barrier
Glucose and amino acids cross slowly
Non-polar/lipids cross quickly

Infarction/neoplasm ➔ destroy tight junctions ➔ vasogenic edema

Cushing's Triad of Acute Raised ICP
(Full triad seen in 1/3 of cases)
- Bradycardia (late finding)
- HTN
- Irregular respiratory pattern

Papilledema
- Optic disc swelling with blurred margins (most commonly bilateral)
- Larger blind spot

Investigations
- patients with suspected elevated ICP require an urgent CT/MRI to identify etiology, assess for MLS/herniation
- ICP monitoring where appropriate

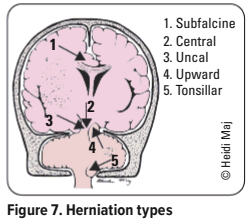


Figure 7. Herniation types

Herniation Syndromes

Table 5. Herniation Syndromes

Herniation Syndrome	Definition	Etiology	Clinical Features
1. Subfalcine	Cingulate gyrus herniates under falx	Lateral supratentorial lesion	Usually asymptomatic Warns of impending transtentorial herniation Risk of anterior cerebral artery (ACA) compression
2. Central Tentorial (Axial)	Displacement of diencephalon through tentorial notch	Supratentorial midline lesion Diffuse cerebral swelling Late uncal herniation	Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla Decreased LOC (midbrain compression), extraocular movement (EOM)/upward gaze impairment ("sunset eyes"): compression of pretectum and superior colliculi (Parinaud's syndrome) Risk of posterior cerebral artery (PCA) compression Brainstem (Duret) hemorrhage: secondary to shearing of basilar artery perforating vessels DI (traction on pituitary stalk and hypothalamus), end-stage sign
3. Lateral Tentoria (Uncal)	Uncus of temporal lobe herniates down through tentorial notch	Lateral supratentorial lesion (often rapidly expanding traumatic hematoma)	Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) + ipsilateral EOM paralysis, ptosis (CN III compression) Decreased LOC (midbrain compression) Risk of PCA compression Contralateral hemiplegia ± extensor (upgoing) plantar response ± ipsilateral hemiplegia ("Kernohan's notch" – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle)
4. Upward	Cerebellar vermis herniates through tentorial incisura	Posterior fossa mass, brainstem or cerebellar infarction, exacerbated by ventriculostomy or ventriculoperitoneal (VP) shunt	Cerebellar infarct (superior cerebellar artery (SCA) compression) Hydrocephalus (cerebral aqueduct of Sylvius compression)
5. Tonsillar	Cerebellar tonsils herniate through foramen magnum	Infratentorial lesion Following central tentorial herniation Following LP in presence of intracranial mass lesion	Neck stiffness and head tilt (tonsillar impaction) Decreased LOC (midbrain compression) Flaccid paralysis Respiratory irregularities, respiratory arrest (compression of medullary respiratory centres) Blood pressure instability (compression of medullary cardiovascular centres)

Treatment of Elevated ICP

- treatment principle: treat primary etiology (i.e. remove mass lesions, ensure adequate ventilation e.g. in acute respiratory distress syndrome (ARDS))
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
- targets: ICP <20 mmHg, CPP 60-70 mmHg, sBP >100 (ages 50-69) or >110 (age <50 or >70) mmHg (but these targets should be individualized based on the patient's clinical picture, progression, and the treating physician's judgment)

Table 6. Management of Elevated ICP

Consideration	Intervention	Rationale
Conservative Measures		
Position	Elevate head of bed at 30° Maintain neck in neutral position	Increases 1. Jugular venous patency 2. Intracranial venous outflow with minimal effect on MAP
Fever Management	Acetaminophen or mechanical cooling	Decreases basal metabolic and oxygen demands in order to minimize brain injury
Prevent Hypotension	PRN: fluid, vasopressors, dopamine, norepinephrine	Maintains CBF
Normocarbia	Ventilate to pCO_2 35-40 mmHg	Prevents vasodilation
Adequate O_2	Target pO_2 >60 mmHg	Prevents hypoxic brain injury
Osmolar Diuresis	Mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6 h to serum osmolarity of 315-320 mOsm/kg Acts in 15-30 min, maintain sBP >100 mmHg Hypertonic saline 3% comparable to mannitol	Increases serum tonicity → osmotically drives fluid out of brain
Corticosteroids	Dexamethasone	Decreases vasogenic edema over subsequent days around brain tumour, abscess, blood No proven value in head injury or stroke
Aggressive Measures		
Sedation	Usually propofol Others: barbiturates/codeine, or fentanyl/$MgSO_4$ Light = barbiturates/codeine Heavy = fentanyl/$MgSO_4$	Reduces sympathetic tone Reduces HTN induced by muscle contraction
Paralysis	Vecuronium	Reduces sympathetic tone Reduces HTN induced by muscle contraction
Barbiturate-Induced Coma (refractory ICP)	Phenobarbital 10 mg/kg over 30 min, then 1 mg/kg q1 h continuous infusion	Reduces CBF and metabolism Decreases mortality, but no effect on neurologic outcome No role for the use of hypothermia in head injury
Hyperventilate	Target pCO_2 30-35 mmHg Avoid within 24 h following trauma	Decreases CBF and thus ICP, but use for brief periods only
Drain CSF	Insert EVD (if acute) or shunt Drain 3-5 mL CSF	Reduces intracranial volume
Decompression	Decompressive craniectomy	Allows brain to swell while reducing risk of herniation

Treatment of Elevated ICP

ICP HEAD
Intubate
Calm (sedate)/Coma
Place drain/Paralysis
Hyperventilate
Elevate head
Adequate BP
Diuretic (mannitol)

Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension
NEJM 2016;375:1119-1130
Purpose: To compare the effect of decompressive craniectomy on clinical outcomes to that of medical management in patients with traumatic brain injury (TBI) and refractory intracranial HTN.
Methods: Patients with TBI and refractory intracranial HTN >25 mmHg were randomized to undergo decompressive craniectomy or receive ongoing medical care. Primary outcome was Extended Glasgow Outcome Scale at 6 mo.
Results: Patients treated with decompressive craniectomy had lower mortality rates (26.9% vs. 48.9%) but higher rates of disability (8.5% vs. 2.1% lower severe disability, 21.9% vs. 14.4% upper severe disability, 15.4% vs. 8.0% moderate disability).
Conclusion: Compared to medical care, decompressive craniectomy in patients with TBI and refractory intracranial HTN results in lower mortality but higher rates of vegetative state and severe disability.

Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)

Definition
- raised ICP with papilledema, but without: mass, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)
- diagnosed by modified Dandy's criteria

Etiology
- unknown (majority), but associated with:
  - vascular: dural venous sinus thrombosis
  - habitus/diet: obesity, hypervitaminosis A
  - endocrine: reproductive age, menstrual irregularities, Addison's/Cushing's disease
  - hematologic: iron deficiency anemia, polycythemia vera
  - drugs: steroid withdrawal, tetracycline, amiodarone, lithium, nalidixic acid, oral contraceptive, growth hormone, retinoids
- risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones ("fat, female, fertile, forties")

Epidemiology
- incidence: general population ~1-2 in 100000 per yr; women of childbearing age with obesity 19-21 in 100000 per yr

Modified Dandy's Criteria
1. Symptoms of raised ICP
2. No localizing signs except CN VI palsy
3. Patient awake and alert
4. Normal neuroimaging without evidence of thrombosis
5. LP opening pressure >25 cm H_2O, normal CSF
6. No better explanation for raised ICP

Clinical Features
- symptoms: H/A in >90%, nausea, transient visual obscurations, pulsatile tinnitus, diplopia can occur with CN VI palsy, neck/back pain
- signs: CN VI palsy can occur (otherwise no neurologic deficits), visual acuity and field deficits, papilledema, optic atrophy
- morbidity: risk of blindness and severe visual impairment (6-24% risk) are the major morbidity of idiopathic intracranial hypertension (IIH), but are not reliably correlated to duration, symptoms, or clinical course
- clinical course: usually self-limited, recurrence in 10%, chronic in some

Investigations
- MRI brain (with and without contrast): slit-like ventricles and distended perioptic subarachnoid space, but otherwise normal
  - rule out: venous sinus thrombosis, mass, infection, hydrocephalus
- LP findings
  - opening pressure >25 cmH_2O
  - normal CSF analysis
- ophthalmologic: fields, acuity, papilledema

Treatment
- lifestyle change: encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic, or furosemide; discontinue any medications contributing to the condition
- surgery: if above fail, serial LPs (temporizing), optic nerve sheath fenestration (if progressive impairment of visual acuity), shunt placement (VP, lumboperitoneal)
- long term: 2 yr follow-up, repeat imaging to rule out occult tumour, ophthalmology follow-up

Effect of Acetazolamide on Visual Function in Patients with Idiopathic Intracranial Hypertension and Mild Visual Loss (IIHTT)
JAMA 2014;311(16):1641-1651
Purpose: To determine whether acetazolamide and a low-sodium weight reduction diet is beneficial in improving vision compared to diet alone in patients with IIH and mild visual loss.
Methods: 165 patients were randomized to either a low-sodium weight-reduction diet plus the maximally tolerated dosage of acetazolamide or placebo for 6 mo.
Results: Acetazolamide was superior to placebo with regards to perimetric mean deviation improvement (P=0.05), papilledema grade improvement (P<0.001), vision-related quality of life (P=0.003), and weight reduction (P<0.001).
Conclusion: Acetazolamide with low-sodium weight-reduction diet resulted in improvement in visual field function in patients with IIH and mild visual loss.

Hydrocephalus

- for hydrocephalus in children, see *Pediatric Neurosurgery, NS42*

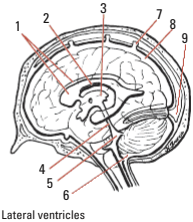
Definition
- accumulation of excess CSF in the brain; hydrocephalus is functionally divided into obstructive and communicating
  - flow of CSF: produced by choroid plexus, lateral ventricles → foramen of Monro → 3rd ventricle → cerebral aqueduct of Sylvius → 4th ventricle → foramen of Luschka (lateral) and Magendie (medial) → subarachnoid space where CSF is reabsorbed by arachnoid villi/granulations into dural venous sinuses

Classification

Table 7. Classification of Hydrocephalus

Disorder	Definition	Etiology	Findings on CT/MRI
Obstructive (Non-Communicating) Hydrocephalus	CSF circulation blocked within ventricular system proximal to the arachnoid granulations	**Acquired** **Aqueductal stenosis**: adhesions after infection, hemorrhage; gliosis, tumour (e.g. pontine glioma) **Intraventricular lesions**: tumours, (e.g. 3rd ventricle colloid cyst, hematoma), mass causing tentorial herniation causing aqueduct/4th ventricle compression **Posterior fossa lesions**: tumours, (e.g. brain metastasis, medulloblastoma, ependymoma compromising 4th ventricle) **Others**: neurosarcoidosis, abscess/granulomas, arachnoid cysts **Congenital**: Primary aqueductal stenosis, Dandy-Walker malformation, Arnold-Chiari malformation, myelomeningocele, encephalocele (see *Pediatric Neurosurgery, NS41*)	Ventricular enlargement proximal to block (enlarged temporal horns, ballooning frontal and/or occipital horns, enlarged 3rd ± 4th ventricles = triventricular hydrocephalus) Periventricular hypodensity/lucency (transependymal migration of CSF forced into extracellular space) Sulcal effacement, reduced visibility of Sylvian and interhemispheric fissures
Non-Obstructive (Communicating) Hydrocephalus	Most commonly CSF absorption blocked at extraventricular site = arachnoid granulations, rarely CSF absorption is overwhelmed by increased production	Post-infectious (#1 cause) → meningitis, abscess, cysticercosis Post-hemorrhagic (#2 cause) → SAH, IVH, traumatic Leptomeningeal carcinomatosis – metastatic meningitis Choroid plexus papilloma Idiopathic → NPH	All ventricles dilated
NPH	Persistent ventricular dilation in the context of normal CSF pressure	Idiopathic (50%) Others: SAH, meningitis, trauma, radiation-induced	Enlarged ventricles without increased prominence of cerebral sulci
Hydrocephalus *Ex Vacuo*	Ventricular enlargement resulting from atrophy of surrounding brain tissue	Normal aging Degenerative dementias: Alzheimer's, frontotemporal, Creutzfeldt-Jakob disease (see Neurology, N27)	Enlarged ventricles and sulci Cerebral atrophy

CSF production = CSF reabsorption = ~ 500 mL/d in normal adults
Normal CSF volume ~150 mL (50% spinal, 50% intracranial → 25 mL intraventricular, 50 mL subarachnoid)



1. Lateral ventricles
2. Choroid plexus
3. Third ventricle
4. Cerebral aqueduct (of Sylvius)
5. Fourth ventricle
6. Foramina of Luschka and Magendie
7. Arachnoid granulations
8. Subarachnoid space
9. Confluence of sinuses (torcula)

© Kari Francis 2004

Figure 8. The flow of CSF

Etiology
- impaired CSF dynamics
  - obstruction of CSF flow
  - decreased CSF absorption
  - increased CSF production (rarely in choroid plexus papilloma 0.4-1% of intracranial tumours)
- congenital and acquired causes

Epidemiology
- estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2 in 1000 live births

Clinical Features
- acute hydrocephalus: signs and symptoms of acutely elevated ICP (see *Table 4, NS7*)
- chronic/gradual onset hydrocephalus (wk to mo; i.e. NPH): presents with a classic triad (Hakim's triad)
  - ataxia (magnetic gait) + apraxia (pressure of ventricle on lower extremity motor fibres → gait disturbance)
  - incontinence (pressure on cortical bowel/bladder centre)
  - dementia (subcortical)

Classic (Hakim's) Triad of NPH Progression
"Wet, wacky, wobbly": Incontinence, dementia, ataxia

Investigations
- imaging
  - CT/MRI findings (see *Table 7, NS9*)
  - ultrasound (through anterior fontanelle in infants): ventriculomegaly, size and location of lesions (e.g. IVH)
  - mantle radionuclide cisternography can test CSF flow and absorption rate (unreliable)
- ICP monitoring (e.g. LP, EVD) may be used to investigate NPH and test response to shunting (lumbar tap test)

Important Features to Note on CT and MRI (± contrast enhancement)
- Lesions (± edema, necrosis, hemorrhage)
- MLS and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)

Treatment
- EVD (acute hydrocephalus, intraventricular hemorrhage)
- intermittent LPs for transient communicating hydrocephalus (SAH, IVH in premature infants)
- eliminating obstruction (i.e. excision of mass, posterior fossa decompression for Chiari malformation)
- endoscopic
  - endoscopic third ventriculostomy (ETV) ± choroid plexus cauterization (for obstructive hydrocephalus)
  - endoscopic placement of aqueductal stent
- shunt
  - VP: most common shunt
  - ventriculopleural
  - ventriculoatrial (VA)
  - lumboperitoneal: for communicating hydrocephalus and pseudotumour cerebri

Complications of Specific Hydrocephalus Treatments
1. VP Shunt: intra-abdominal cysts, adhesions, ascites
2. VA Shunt: greater infection risk, septicemia, emboli
3. Ventriculopleural Shunt: pleural effusion, hydrothorax, respiratory distress
4. LP Shunt: radiculopathy, CSF leaks, adhesions, arachnoiditis
5. ETV: 56% success rate, hypothalamic injury, iatrogenic basilar aneurysm

Shunt Complications

Table 8. Shunt Complications

Complication	Etiology	Clinical Features	Investigations
Obstruction (most common) Proximal Catheter Valve Distal Catheter	Obstruction by choroid plexus Buildup of proteinaceous accretions, blood, cells (inflammatory or tumour) Infection Disconnection or damage	Acute hydrocephalus signs and symptoms of increased ICP	"Shunt series" (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration) CT Radionuclide "shuntogram"
Infection (3-6%)	*S. epidermidis* *S. aureus* *P. acnes* Gram-negative bacilli	Fever, N/V, anorexia, irritability Meningitis Peritonitis Signs and symptoms of shunt obstruction Shunt nephritis (VA shunt)	CBC Blood culture Tap shunt for C&S (LP usually NOT recommended)
Overshunting (10% over 6.5 yr)	Slit ventricle syndrome, collapse of ventricles leading to occlusion of shunt ports by ependymal lining	Chronic or recurring H/A often relieved when lying down	CT/MRI Slit-like ventricles on imaging
	SDH Collapsing brain tears bridging veins (especially common in NPH patients)	Asymptomatic H/A, vomiting, somnolence	CT
	Secondary craniosynostosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus	Abnormal head shape	Clinical CT
Seizures (5.5% risk in 1st yr, 1.1% after 3rd yr)	Ventricular shunts only		EEG
Inguinal hernia (13-15% incidence when shunt inserted in childhood)	Increased intraperitoneal pressure/fluid results in hernia becoming apparent	Inguinal swelling, discomfort	U/S

Spontaneous Intracranial Hypotension

Definition
- low CSF pressure + postural headache secondary to CSF leak
- symptoms not attributable to another disorder, no recent history of dural puncture

Etiology
- CSF leakage from the thecal sac within or along the spinal canal

Epidemiology
- incidence: ~2-5 in 100000 per yr, but likely underdiagnosed; M:F=1:2
  - can occur at any age, but most frequently in 4th or 5th decade

Clinical Features
- **symptoms**: orthostatic H/A in 75-80%, tinnitus or auditory disturbance ("underwater feeling") in 50%, dizziness in 50%, N/V, photophobia, meningismus
- **signs**: CN III, CN IV, CN VI palsy in <10%
- **morbidity**: misdiagnosis and underdiagnosis are common, leading to delays in treatment and inappropriate treatment for mimickers of intracranial hypotension
- **clinical course**: usually self-limited, recurrence in 10%, chronic in some

Investigations
- MRI brain with contrast: sagging of the brain (e.g. low cerebellar tonsils), pachymeningeal enhancement, subdural hematoma or hygroma, pituitary hyperemia
- MRI spine with contrast: extrathecal fluid collections/extrathecal contrast accumulation and/or meningeal diverticula
- CT myelogram with contrast: preferred method to diagnose and localize CSF leak
  - digital subtraction myelogram (DSM): combines fluoroscopy and ability to subtract background images to visualize small CSF leaks by contrast extravasation
- LP: opening pressure <6 cmH_2O; xanthochromia, elevated protein, lymphocytic pleocytosis

Treatment
- conservative management: bed rest, hydration, caffeine, possibly theophylline
- epidural blood patch: mainstay treatment; autologous blood (10-20 mL) injected into epidural space
- surgery: indicated if epidural blood patches are ineffective and site of leak has been localized

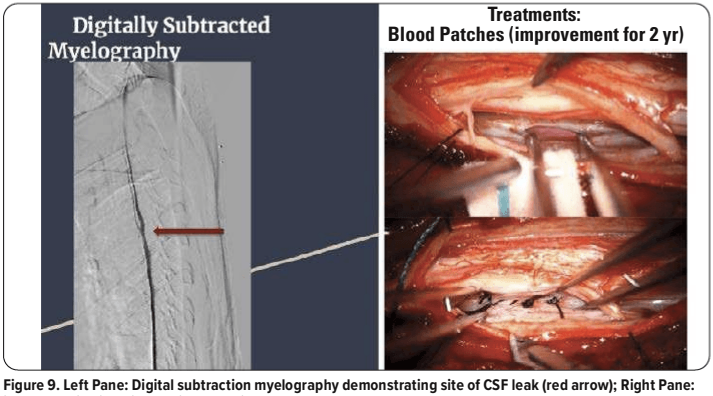


Figure 9. Left Pane: Digital subtraction myelography demonstrating site of CSF leak (red arrow); Right Pane: intraoperative imaging of direct repair of the dura

Figure courtesy of Dr. Eric M. Massicotte

CNS Tumours

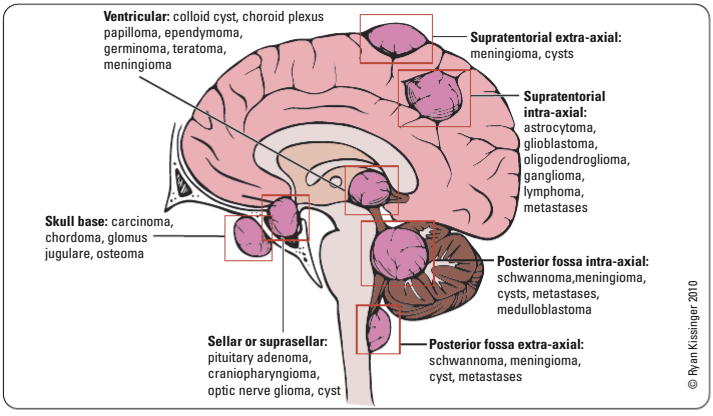

Ventricular: colloid cyst, choroid plexus papilloma, ependymoma, germinoma, teratoma, meningioma
Supratentorial extra-axial: meningioma, cysts
Supratentorial intra-axial: astrocytoma, glioblastoma, oligodendroglioma, ganglioma, lymphoma, metastases
Skull base: carcinoma, chordoma, glomus jugulare, osteoma
Posterior fossa intra-axial: schwannoma,meningioma, cysts, metastases, medulloblastoma
Sellar or suprasellar: pituitary adenoma, craniopharyngioma, optic nerve glioma, cyst
Posterior fossa extra-axial: schwannoma, meningioma, cyst, metastases
© Ryan Kissinger 2010

Figure 10. Tumours of the CNS

Classification

- benign vs. malignant, primary vs. metastatic (e.g. primary in breast, lung), intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, but can be devastating due to mass effect in fixed volume of skull (e.g. most meningiomas)
- malignant: implies rapid growth, invasiveness, possibly drop-metastases to spinal cord from a primary CNS tumour (rare)
- Based on the 2021 WHO Classification of Tumours of the CNS guideline which integrates molecular diagnostics with other diagnostic approaches (i.e. immunohistochemistry, histology)

Table 9. WHO 2021 Classification of Tumours of the CNS

Gliomas, Glioneuronal Tumours, Neuronal Tumours	
Adult-type diffuse gliomas	Astrocytoma, IDH-mutant Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted Glioblastoma, IDH-wildtype
Pediatric-type diffuse low-grade gliomas	Diffuse astrocytoma, *MYB*- or *MYBL1*-altered Angiocentric glioma Polymorphous low-grade neuroepithelial tumour of the young Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high-grade gliomas	Diffuse midline glioma, H3K27-altered Diffuse hemispheric glioma, H3G34-mutant Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype Infant-type hemispheric glioma
Circumscribed astrocytic gliomas	Pilocytic astrocytoma High-grade astrocytoma with piloid features Pleomorphic xanthoastrocytoma Subependymal giant cell astrocytoma Chordoid glioma Astroblastoma, *MN1*-altered
Glioneuronal and neuronal tumours	Ganglioglioma Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma Dysembryoplastic neuroepithelial tumour Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters Papillary glioneuronal tumour Rosette-forming glioneuronal tumour Myxoid glioneuronal tumour Diffuse leptomeningeal glioneuronal tumour Gangliocytoma Multinodular and vacuolating neuronal tumour Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) Central neurocytoma Extraventricular neurocytoma Cerebellar liponeurocytoma
Ependymal tumours	Supratentorial ependymoma (including *ZFTA* fusion-positive or *YAP1* fusion-positive) Posterior fossa ependymoma (including group PFA and PFB) Spinal ependymoma (including *MYCN*-amplified) Myxopapillary ependymoma Subependymoma

DDx for Ring Enhancing Lesion on CT with Contrast

MAGICAL DR
Metastases*
Abscess*
Glioblastoma (high-grade glioma)*
Infarct
Contusion
AIDS (toxoplasmosis)
Lymphoma
Demyelination
Resolving hematoma, Radiation Necrosis
(*3 most common diagnoses)

Ring Enhancing Lesions in Patients with HIV
DDx: Toxoplasmosis or CNS lymphoma
Treatment: Empiric treatment with pyrimethamine and sulfadiazine; brain biopsy if no resolution with antimicrobial therapy
Primary CNS lymphoma reported in 6-20% of HIV infected patients

Primary Brain Tumours
Rarely undergo metastasis
Adults = mostly supratentorial
Children = mostly infratentorial

Table 9. WHO 2021 Classification of Tumours of the CNS

Choroid Plexus Tumours	
Choroid plexus papilloma Atypical choroid plexus papilloma Choroid plexus carcinoma	
Embryonal Tumours	
Medulloblastoma	Medulloblastomas, molecularly defined: WNT-activated, SHH-activated and *TP53*-wildtype, SHH-activated and *TP53*-mutant, non-WNT/non-SHH Medulloblastomas, histologically defined
Other CNS embryonal tumours	Atypical teratoid/rhabdoid tumour Cribriform neuroepithelial tumour Embryonal tumour with multilayered rosettes CNS neuroblastoma, *FOXR2*-activated CNS tumour with *BCOR* internal tandem duplication CNS embryonal tumour
Pineal Tumours	
Pineocytoma Pineal parenchymal tumour of intermediate differentiation Pineoblastoma Papillary tumour of the pineal region Desmoplastic myxoid tumour of the pineal region, *SMARCB1*-mutant	
Cranial and Paraspinal Nerve Tumours	
Schwannoma Neurofibroma Perineurioma Hybrid nerve sheath tumour Malignant melanotic nerve sheath tumour Malignant peripheral nerve sheath tumour Paraganglioma	
Meningiomas	
Mesenchymal, Non-Meningothelial Tumours	
Soft tissue tumours	Fibroblastic and myofibroblastic tumours: solitary fibrous tumour Vascular tumours: haemangiomas and vascular malformations, hemangioblastomas Skeletal muscle tumours: rhabdomyosarcoma Uncertain differentiation: intracranial mesenchymal tumour, *FET-CREB* mutation positive, *CIC*-rearranged sarcoma, primary intracranial sarcoma, *DICER1*-mutant, Ewing sarcoma
Chondro-osseous tumours	Chondrogenic tumours: mesenchymal chondrosarcoma, chondrosarcoma Notochordal tumours: chordoma (including poorly differentiated chordoma)
Melanocytic Tumours	
Diffuse meningeal melanocytic neoplasms	Meningeal melanocytosis Meningeal melanomatosis
Circumscribed meningeal melanocytic neoplasms	Meningeal melanocytoma Meningeal melanoma
Hematolymphoid Tumours	
Lymphomas	CNS lymphomas: primary diffuse large B-cell lymphoma of the CNS, immunodeficiency-associated CNS lymphoma, lymphomatoid granulomatosis, intravascular large B-cell lymphoma Miscellaneous rare lymphomas in the CNS: MALT lymphoma of the dura, other low-grade B-cell lymphomas of the CNS, anaplastic large cell lymphoma (*ALK*+/*ALK*-), T-cell and NK/T-cell lymphomas
Histiocytic tumours	Erdheim-Chester disease Rosai-Dorfman disease Juvenile xanthogranuloma Langerhans cell histiocytosis Histiocytic sarcoma
Germ Cell Tumours	
Teratoma: mature, immature, somatic-type malignancy Germinoma Embryonal carcinoma Yolk sac tumour Choriocarcinoma Mixed germ cell tumour	
Tumours of the Sellar Region	
Adamantinomatous craniopharyngioma Papillary craniopharyngioma Pituicytoma, granular cell tumour of the sellar region, and spindle cell oncocytoma Pituitary adenoma/PitNET Pituitary blastoma	
Metastases to the CNS	
Metastases to the brain and spinal cord parenchyma Metastases to the meninges	

Familial Syndromes Associated with CNS Tumours

- ataxia telangiectasia
- Cowden syndrome
- familial adenomatous polyposis
- hereditary non-polyposis-related colorectal cancer
- Li-Fraumeni syndrome
- Gorlin syndrome
- neurofibromatosis types 1 & 2
- multiple endocrine neoplasia type 1
- tuberous sclerosis complex
- von Hippel-Lindau disease
- Turcot syndrome
- Lynch syndrome

New onset communicating hydrocephalus in a patient with cancer should raise the suspicion of leptomeningeal carcinomatosis

Investigations

- CT, MRI with contrast, stereotactic biopsy (tissue diagnosis and molecular markers for prognosis), tumour resection (often performed as initial step rather than biopsy), metastatic workup, tumour markers (i.e. germ cell tumours)

Treatment

- conservative: serial history, physical, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce ICP, cytotoxic cerebral edema; pharmacologic (i.e. pituitary adenoma)
- surgical: total or partial excision (decompressive, palliative)
- radiotherapy: conventional fractionated XRT, hypofractionated XRT, SRS (e.g. Gamma Knife)
- chemotherapy: e.g. alkylating agents (i.e. temozolomide, vincristine, cyclophosphamide, etc.)
- targeted therapy: e.g. trastuzumab for HER2-positive breast cancer and brain metastases, osimertinib for EGFR-mutant lung cancer and brain metastases

Table 10. Tumour Location: Etiology and Clinical Features

	Supratentorial	Infratentorial (Posterior Fossa)
Epidemiology		
Age <15 yr Incidence: 2-5 in 100000 per yr 60% infratentorial	Glioma (all grades) (50%) Craniopharyngioma (2-5%) Others: pineal region tumours, choroid plexus tumours, ganglioglioma, dysembryoplastic neuroepithelial tumours (DNET)	Medulloblastoma (15-20%) Cerebellar astrocytoma (15%) Ependymoma (9%) Brainstem astrocytoma
Age >15 yr 80% supratentorial	High-grade glioma (12-15%, e.g. Glioblastoma Multiforme - GBM) Metastasis (15-30%, includes infratentorial) Meningioma (15-20%) Low-grade astrocytoma (8%) Pituitary adenoma (5-8%) Oligodendroglioma (5%) Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts	Metastasis Acoustic neuroma (schwannoma) (5-10%) Hemangioblastoma (2%) Meningioma
Clinical Features		
Shared Features (from elevated ICP)	**H/A**: usually worse in AM and made worse with straining, coughing **N/V** **Papilledema** **Diplopia** - CN VI palsy	
Distinguishing Features	**Seizure**: commonly the first symptom Progressive neurological deficits (70%) **Frontal lobe**: hemiparesis, dysphasia, personality changes, cognitive changes **Temporal lobe**: auditory/olfactory hallucinations, memory deficits, contralateral superior quadrantanopia **Mental status change**: depression, apathy, confusion, lethargy "Tumour TIA" (transient ischemic attack) stroke like symptoms caused by a) occlusion of vessel by tumour cells b) hemorrhage c) 2° to "steal phenomenon" - blood is shunted from ischemic regions to non-ischemic regions Endocrine disturbance: pituitary tumours (see Endocrinology, E23)	**Brainstem involvement**: CN deficits and long tract signs **N/V**: compression on vagal nucleus/area postrema **Diplopia**: direct compression CN VI **Vertigo** **Nystagmus** **Truncal ataxia + titubation**: cerebellar vermis lesions **Limb ataxia, dysmetria, intention tremor**: cerebellar hemisphere lesions **Obstructive hydrocephalus** more common than supratentorial lesions

Metastatic Tumours

Brain Metastasis

- most common intracranial tumour in adults (~50% of all brain tumours)
- afflict ~25% of patients with any cancer
- hematogenous spread most common
- 80% are hemispheric, often at grey-white matter junction or temporal-parietal-occipital lobe junction
  - likely emboli spreading to terminal middle cerebral artery (MCA) branches

Investigations

- identify primary tumour
  - full metastatic workup (CXR, CT chest/abdomen, abdominal U/S, nuclear medicine scan/PET, mammogram)
- CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
- contrast-enhanced MRI more sensitive, especially for posterior fossa
- consider biopsy/resection in unusual cases or if no primary tumour identified

Treatment

- medical
  - phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  - dexamethasone to reduce edema given with H2 blocker
  - role of chemotherapy limited because of poor penetration across BBB
  - targeted therapies are currently being investigated (e.g. EGFR (epidermal growth factor receptor) inhibitors in patients with EGFR-mutant lung cancer and brain metastases)
  - immunotherapy (currently under investigation)
- radiation
  - SRS (highly focused fraction of radiation targeted to tumour): for discrete, deep-seated/inoperable tumours
  - multiple lesions: use WBRT (>10 lesions); consider SRS (≤10 lesions)
  - postoperative adjuvant radiotherapy consideration: SRS to surgical cavity following resection
  - emerging evidence supports avoidance of WBRT and use of focal radiation to spare cognitive functions (refer to Brown et al., 2016)
- surgical
  - single/solitary lesions or dominant lesion with significant mass effect or symptoms: surgical resection and radiation in carefully selected patients
  - emerging: SRS prior to surgical resection (neoadjuvant XRT - through to reduce risk of local leptomeningeal dissemination during surgical resection)

Prognosis

- median survival without treatment once symptomatic is ~1 mo, with optimal treatment 6-9 mo; may be prolonged survival in some patient subgroups (e.g. HER2/neu breast cancer, EGFR-mutant lung cancer)
- the disease-specific Graded Prognostic Assessment (DS-GPA) is a useful prognostic index
- depending on primary tumour type, prognosis may depend on a combination of patient age, Karnofsky score, extent of extracranial metastatic disease, number of intracranial lesions, and molecular disease subtype

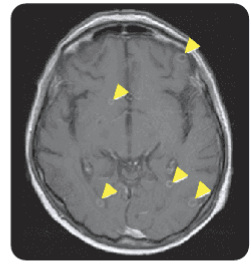
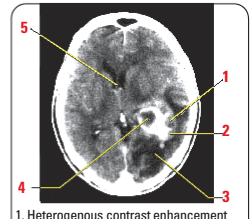


Figure 11. Multiple brain metastases (see arrows)

Most Common Cancers that Metastasize to the CNS

Site of Primary	Frequency of CNS metastasis
Lung	44%
Breast	10%
Kidney (RCC)*	7%
GI	6%
Melanoma	3%

*RCC=renal cell carcinoma



1. Heterogenous contrast enhancement
2. Ill-defined borders (infiltrative)
3. Peritumoural edema
4. Central necrosis
5. Compression of ventricles, midline shift

Figure 12. High-grade glioma on CT

Adult Diffuse Gliomas

- most common primary intra-axial brain tumour, common in 4th-6th decades

Table 11. WHO 2021 Diffuse Gliomas Classification

Type	WHO Grade*	Typical CT/MRI Findings	Altered Molecular Profiles	Prognosis
Oligodendroglioma	**2, 3**	Low grade: areas of calcification on CT, ± enhancement High grade: enhancement	Defining: IDH-mutant Other: TERT promoter, CIC, FUBP1, NOTCH1	Low grade: ~10 yr High grade: 5 yr
Astrocytoma	**2, 3, 4**	Low grade: mass effect, no enhancement High grade: complex enhancement	Defining: IDH mutant and 1p/19q codeleted Other: ATRX, TP53, CDKN2A/B	Low grade: 3 yr High grade: 1.5-2 yr
Glioblastoma	**4**	Necrosis (ring enhancement)	Defining: IDH-wildtype Other: TERT promoter, chromosomes 7/10, EGFR	15 mo

*grade based on natural history

Surgical Resection vs. Watchful Waiting in Low-Grade Gliomas
Ann Oncol 2017;28:1942-1948
Purpose: This study examined the effect of up-front surgery vs. watchful waiting for treatment of low-grade gliomas on long term survival.
Methods: The study was designed as a population-based parallel cohort study that compared outcomes from a hospital favouring watchful waiting (n=66 patients) and one favouring early resection (n=87 patients). Follow-up was between 7 and 18 yr post-diagnosis. The two groups were equivalent in terms of baseline parameters.
Results: Overall, survival was significantly better with early surgical resection. Patients from the centre favouring watchful waiting had a median survival of 5.8 yr (95% CI 4.5-7.2) whereas patients from the centre favouring early resection had a median survival of 14.4 yr (95% CI 10.4-18.5). The enhanced survival benefit remained after adjusting for molecular markers.
Conclusions: Early surgical resection of low-grade gliomas is associated with significantly improved overall survival compared to watchful waiting.

Clinical Features
- sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
- symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

Investigations
- CT/MRI with contrast: variable appearance depending on grade
  - hypodense on CT, hypointense on T1 MRI, hyperintense on T2 MRI
  - low-grade: most do not enhance and have calcification on CT
  - high-grade: most enhance with CT contrast dye/gadolinium, possibly with central necrosis (especially if IDH wildtype)
  - histology during surgical resection or biopsy

Treatment
- **low-grade diffuse gliomas**
  - close follow-up, radiation, chemotherapy, and surgery are all valid options
  - dedifferentiation to more malignant grade; typically occurs faster when diagnosed after age 45
  - surgery: maximal safe resection, not curative, trend towards better outcomes, provides tissue sample for histologic/molecular characterization
    - early surgery is recommended for oligodendroglioma, with treatment including XRT and PCV (chemotherapy regimen)
    - early surgery is recommended for astrocytomas, with treatment including radiation therapy and TMZ
  - XRT alone or postoperative prolongs survival (retrospective evidence)
  - chemotherapy: initial therapy in all patients with high-risk low-grade glioma
- **high-grade diffuse gliomas**
  - goal is to prolong "quality" survival
  - surgery
    - gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant TMZ
      - except: nearing end-of-life; or extensive brainstem, bilateral, or dominant lobe GBM involvement
    - awake craniotomy for tumours in "eloquent" regions (e.g. speech and language regions or near motor strip)
    - stereotactic biopsy if resection not possible, followed by fractionated radiation with 2 cm margin
      - expectant: based on functional impairment Karnofsky score <70; patient's/family's wishes
  - chemotherapy: TMZ (agent of choice); better response to TMZ predicted by MGMT gene methylation
- **multicentric gliomas**
  - WBRT ± chemotherapy

Primary Central Nervous System Lymphoma

- highly aggressive, non-Hodgkin lymphoma confined to the CNS; ~95% are large B-lymphocyte
- brain + spinal cord, leptomeningeal, CSF, and ocular manifestations possible
- intracranial lesions predominantly supratentorial

Clinical Features
- occurs in both immunocompetent and immunocompromised populations (multifocal lesions in 20-40% of immunocompetent patients, and in 30-80% of immunocompromised patients)
- epidemiology: 0.47 in 100000 per yr; M:F=1.35:1; age of onset 50-70 (30-40 in immunocompromised individuals)
- symptoms: focal neurological deficit, cognitive/behavioural symptoms ± increased ICP or seizures or CN palsies
  - blurred vision + floaters if ocular involvement
- high association with Epstein-Barr virus in patients with HIV

Investigations
- CT: hyper- or iso-attenuated lesions; significant enhancement with contrast
- MRI with contrast (imaging of choice): intensely enhancing lesions, often localized to periventricular space
  - immunocompetent → homogenous enhancement ± minimal edema
  - immunocompromised → heterogenous or ring enhancement, necrosis, edema ± hemorrhage
  - restriction on diffusion imaging due to hypercellularity helpful to distinguish from other brain tumours
- confirmation by stereotactic biopsy and histopathology
  - corticosteroids may prevent histopathological diagnosis → avoid until biopsy complete when clinically possible

Treatment
- chemotherapy: first-line treatment; induction therapy using MATRix regimen (high-dose methotrexate (HDMTX) + cytarabine + thiotepa + rituximab) preferred
- surgery: generally reserved for stereotactic biopsy; resection discouraged

Comparison of a Strategy Favouring Early Surgical Resection vs. a Strategy Favouring Watchful Waiting in Low-Grade Gliomas
JAMA 2012;308(18):1881-1888
Purpose: To examine "watchful waiting" vs. early surgical resection of low-grade gliomas.
Study: A population-based parallel cohort study was undertaken between two hospitals that each favoured different management approaches for low-grade gliomas (biopsy and watchful waiting vs. early surgical resection).
Results: 66 patients were included from the watchful waiting hospital and 87 patients from the early resection centre. Median follow-up was 7.0 and 7.1 yr at each centre. The two groups were equivalent in terms of baseline parameters. Overall, survival was significantly better with early surgical resection (watchful waiting: median survival of 5.9 yr 95% CI, 4.5-7.3 vs. early resection: median survival was not reached due to prolonged length of life, P<0.01).
Conclusions: Early surgical resection of low-grade-gliomas is associated with better overall survival as compared to watchful waiting.

Bevacizumab Plus Radiotherapy-Temozolomide for Newly Diagnosed Glioblastoma
NEJM 2014;370:709-722
Purpose: To evaluate the effect of combined bevacizumab and XRT-temozolomide in the treatment of newly diagnosed glioblastoma.
Methods: Patients with supratentorial GBM were randomly assigned to receive IV bevacizumab (n=458) or placebo plus XRT and oral temozolomide (n=463) for 30 wk total in cycles, followed by bevacizumab or placebo monotherapy. Outcomes were progression-free survival and overall survival.
Results: The median progression-free survival was longer in the bevacizumab group compared with placebo (10.6 mo vs. 6.2 mo, HR 0.64, 95% CI 0.55-0.74), although overall survival did not differ significantly between groups (HR 0.88, 95% CI 0.76-1.02). Baseline health-related quality-of-life and performance status were maintained longer in the bevacizumab group although there was a higher frequency of adverse events.
Conclusions: The addition of bevacizumab to XRT-temozolomide improves progression-free survival but not overall survival in patients with glioblastoma.

Interim Results from the CATNON trial (EORTC study 26053-22054) of Treatment with Concurrent and Adjuvant tImozolomide for 1p/19q Non-co-deleted Anaplastic Glioma: a phase 3, randomised, open-label intergroup study
Lancet 2017;390(10103):1645-53
Purpose: To assess the use of radiotherapy with concurrent and adjuvant temozolomide in adults with non-co-deleted anaplastic gliomas.
Methods: Patients with newly diagnosed non-co-deleted anaplastic glioma were randomized to receive radiotherapy alone or with adjuvant temozolomide; or to receive XRT with concurrent temozolomide 75 mg/d, with or without adjuvant temozolomide. The primary endpoint was overall survival.
Results: Overall survival at 5 years was 55·9% (95% CI 47·2–63·8) with and 44·1% (36·3–51·6) without adjuvant temozolomide. Grade 3–4 adverse events were seen in 8–12% of 549 patients assigned temozolomide, and were mainly haematological and reversible.
Conclusions: Adjuvant temozolomide chemotherapy was associated with a significant survival benefit in patients with newly diagnosed non-co-deleted anaplastic glioma.

- radiation: WBRT used in consolidation therapy and for palliation; consider as second-line induction therapy in HDMTX-ineligible patients
  - significant risk of neurotoxicity when combined with HDMTX

Prognosis
- age and performance status are key prognostic factors
- median survival: 26 mo across all age groups; <7 mo for patients ≥70 y/o

Meningioma

- most common **primary** intracranial tumour, arising from arachnoid cap cells
- sometimes calcified, often causes hyperostosis of adjacent bone (detectable on imaging)
- classically see Psammoma bodies ("meningocytic whorls") on histology
- location: 70% occur along the parasagittal convexity, falx cerebri, and sphenoid bone; other locations: tuberculum sellae, foramen magnum, olfactory groove, and CPA

Clinical Features
- middle aged, slight female predominance (M:F=1:1.8), many express the progesterone receptor (increase in size with pregnancy)
- many are asymptomatic and can be an incidental finding; when symptoms occur focal neurologic deficits specific to location, ± seizures, symptoms of increased ICP
- molecular changes: between 40-80% of meningiomas contain mutations in chromosome 22 (involved in suppressing tumour growth); some have extra copies of *PDGFR* and *EGFR*; some are associated with mutations in the Neurofibromatosis Type 2 (*NF2*) gene

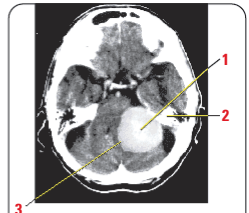
Investigations
- CT with contrast: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed, usually solitary (10% multiple, likely with loss of *NF2* gene/22q12 deletion)
- MRI with contrast: characterization of mass and provides a better assessment of the patency of dural venous sinuses
- angiography
  - most are supplied by external carotid feeders (meningeal vessels)
  - can assess venous sinus involvement, "tumour blush" commonly seen (prolonged contrast image)

Treatment
- conservative management: asymptomatic and/or non-progressive on CT/MRI serial monitoring for interval growth changes
- surgery: often curative if complete resection and indicated when symptomatic and/or documented growth on serial CT/MRI
- endovascular: embolization for highly vascularized, likely bloody, tumours to facilitate surgery
- radiation: SRS is an option for lesions <3 cm and may be considered an alternative in older patients or in cases in which surgical risks are high (deep tumour location, medical comorbidities); SRS should be considered as adjuvant therapy for patients with atypical/malignant meningiomas

Prognosis
- 5 yr survival is >85% for Grade I, 60-90% for Grade II, and 35-65% for Grade III
- depends on extent of resection
- Simpson's classification: degree of surgical resection completeness with symptomatic recurrence

Table 12. Simpson Grade of Meningioma Resection

Grade	Criteria
I	Macroscopically complete removal of tumour, with excision of its dural attachment and of any abnormal bone
II	Macroscopically complete removal of tumour, with coagulation of its dural attachment
III	Macroscopically complete removal of tumour without resection or coagulation of dural attachment or extradural extensions
IV	Partial removal of tumour
V	Simple decompression with or without biopsy



1. Homogenous contrast enhancement
2. Dural attachment
3. Distinct margins

Figure 13. Meningioma on CT

WHO Classification of Meningioma (by histology)
Grade 1: low-risk of recurrence
Grade 2: intermediate risk of recurrence
Grade 3: high-risk of recurrence

Recommendations for Management of Meningiomas
Lancet Oncol 2016;17(9):e383-391
European Association of Neuro-Oncology assessed available literature, rated scientific evidence, and graded recommendation levels.
Key recommendations:
1. First standard therapy is gross total surgical resection (including involved dura).
2. Alternative treatments include radiosurgery for small tumours and fractionated XRT in large/previously treated tumours.
3. New treatment concepts combining surgery and radiosurgery/fractionated XRT to treat complete tumour volume are being developed.
4. Although pharmacological treatments are still experimental, antiangiogenic drugs, peptide receptor radionuclide therapy, and targeted agents are candidates for future pharmacological approaches to treat refractory meningioma of all WHO grades.

Vestibular Schwannoma (Acoustic Neuroma)

- slow-growing (60% show no growth over 1 yr; average rate for growing tumours 1-2 mm/yr), benign posterior fossa tumour (8-10% of tumours)
- arises from vestibular nerve of CN VIII in internal auditory canal, expanding into bony canal and CPA
- if bilateral, diagnostic of NF2
- epidemiology: 1.5 in 100000; all age groups affected, peaks at 4th-6th decades
- often identified in setting of unilateral tinnitus/hearing loss

Clinical Features
- early clinical triad (tumour <2 cm): unilateral progressive hearing loss 98%, tinnitus, and disequilibrium (compression of CN VIII)

Progressive unilateral or asymmetrical sensorineural hearing loss = vestibular schwannoma until proven otherwise

- later clinical features
  - tumour usually >2 cm: otalgia, facial numbness + weakness, changes to taste (due to CN V and VII compression, respectively)
  - tumour usually >4 cm: ataxia, H/A, N/V, diplopia, cerebellar signs (due to brainstem compression; ± obstructive hydrocephalus)

Investigations
- MRI with gadolinium or T2 fast imaging employing steady-state acquisition (FIESTA) sequence (>98% sensitive/specific); CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

Treatment
- expectant: serial imaging (CT/MRI q6 mo) and audiometry if tumour is small, hearing is still preserved, high perioperative risk, or elderly patient
- radiation: SRS for lesions <3 cm
- surgery: if lesion >3 cm, brainstem compression, edema, hydrocephalus
- curable if complete resection (almost always possible, but comes with risk of facial nerve dysfunction)
- operative complications: CSF leak, meningitis, required shunt; CN V, VII, VIII dysfunction (proportional to tumour size; only significant CN VIII disability if bilateral)
- genetic testing and counseling should be considered for family members of *NF2 mutation* carriers

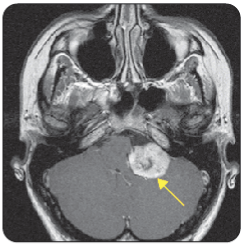


Figure 14. Vestibular schwannoma (tumour in CPA)

Pituitary Adenoma

- primarily from anterior pituitary, 3rd-4th decades, M=F, associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome
- incidence in autopsy studies approximately 20%
- classification
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
  - most common functional: prolactinomas, adrenocorticotropic, GH-producing
  - DDx: parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid artery aneurysm

Go Look For The Adenoma Please – GH, LH, FSH, TSH, ACTH, Prolactin
A compressive adenoma in the pituitary will impair hormone production in this order (i.e. GH-secreting cells are most sensitive to compression)

Clinical Features
- mass effects
- H/A
- bitemporal hemianopia (compression of optic chiasm); hydrocephalus (3rd ventricle compression)
- invasive adenomas: CN III, IV, V1, V2, VI palsy (cavernous sinus compression); proptosis and chemosis (cavernous sinus occlusion)
- endocrine effects (see Endocrinology, E23)
  - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
  - ACTH production: Cushing's disease, hyperpigmentation
  - GH production: acromegaly/gigantism
  - panhypopituitarism: due to compression of pituitary (hypothyroidism, hypoadrenalism, hypogonadism)
  - DI – rare, except in apoplexy
- pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
  - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, panhypopituitarism and DI
  - CSF rhinorrhea and seizures (rare)
  - signs and symptoms of SAH (rare)

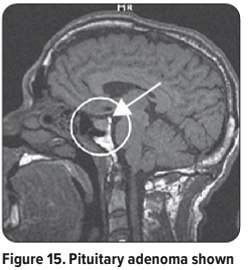
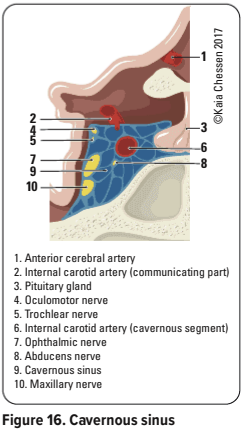


Figure 15. Pituitary adenoma shown with contrast MRI (arrow)
From Miranda-Rius, J., Brunet-LLobet, L., Lahor-Soler, E. et al. GH-secreting pituitary macroadenoma (acromegaly) associated with progressive dental malocclusion and refractory CPAP treatment. Head Face Med 13, 7 (2017). https://doi.org/10.1186/s13005-017-0140-6

Investigations
- formal visual fields, CN testing
- endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose, FSH/LH, insulin-like growth factor 1 (IGF-1)), electrolytes, urine electrolytes, and osmolarity
- imaging (MRI with and without contrast)

Treatment
- medical
  - for apoplexy: rapid corticosteroid administration ± surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing's: serotonin and histamine antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
  - endocrine replacement therapy
- surgical
  - endoscopic endonasal trans-sphenoidal, and less commonly trans-cranial approaches (i.e. for significant suprasellar extension)
- postoperative concerns: DI, adrenal insufficiency (AI), CSF leak



1. Anterior cerebral artery
2. Internal carotid artery (communicating part)
3. Pituitary gland
4. Oculomotor nerve
5. Trochlear nerve
6. Internal carotid artery (cavernous segment)
7. Ophthalmic nerve
8. Abducens nerve
9. Cavernous sinus
10. Maxillary nerve

Figure 16. Cavernous sinus

- DI and AI: AM cortisol, serum sodium and osmolality, urine output and specific gravity (treatment - AI: glucocorticoids; DI: desmopressin/DDAVP™)
- CSF rhinorrhea: test for β-transferrin

Genetic Associations
- sellar masses have known associations with several classic oncogene mutations, including:
  - *MEN1*: loss-of-function mutations are common
  - *GNSA1*: activating mutations found in ~40% of somatotroph adenomas
  - *AIP*: mutations associated with familial pituitary adenomas

Cerebral Abscess

Definition
- pus in brain substance, surrounded by tissue reaction (capsule formation)

Etiology
- modes of spread: 10-60% of patients have no identifiable cause
- pathogens
  - *Streptococcus* (most common), often anaerobic or microaerophilic
  - *Staphylococcus* (penetrating injury)
  - Gram-negatives, anaerobes (*Bacteroides, Fusobacterium*)
  - in neonates: *Proteus* and *Citrobacter* (exclusively)
  - immunocompromised: Toxoplasma, *Nocardia, Candida albicans, Listeria monocytogenes, Mycobacterium,* and *Aspergillus*

Sources of Pus/Infection
- four routes of microbial access to CNS
  1. hematogenous spread: arterial and retrograde venous
     - adults: chest is most common source (lung abscess, bronchiectasis, empyema)
     - children: congenital cyanotic heart disease with R-to-L shunt
     - immunosuppression (AIDS toxoplasmosis)
  2. direct implantation (dural disruption)
     - trauma
     - iatrogenic (e.g. following LP, postoperative)
     - congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
  4. spread from peripheral nervous system (PNS) (e.g. viruses: rabies, herpes zoster)
- common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
    - treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
    - treatment: surgical drainage and antibiotics, 20% mortality
  - meningitis, encephalitis (see Infectious Diseases, ID17)
  - cerebral abscess

Risk Factors
- lung abnormalities (infection, AVFs; especially Osler-Weber-Rendu syndrome/hereditary hemorrhagic telangiectasia)
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of microorganisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess, poor dentition

Clinical Features
- focal neurological signs and symptoms
  - H/A, decreased LOC
- mass effect, increased ICP and sequelae (cranial enlargement in children)
- hemiparesis and seizures in 50% of cases
- ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

Complications
- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

Investigations
- CT scan often first test in emergency department
- MRI
  - imaging of choice
  - restriction on diffusion imaging (also seen in lymphoma)
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)

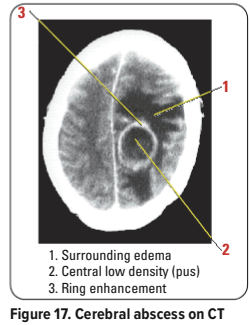


Figure 17. Cerebral abscess on CT

Recommendations for Duration of Antibiotic Therapy for Brain Abscesses
Int J Infect Dis 2010;14Suppl4:S79-92
Systematic literature search using MEDLINE database for studies during 1988-2008 to methodologically evaluate antibiotic therapy duration pertaining to brain abscess.
Key recommendations:
1. Prudent period of 4-6 wk of antibiotic therapy for surgically treated abscesses.
2. 6-8 wk of IV treatment for abscesses treated medically only.
3. 6-8 wk of IV treatment for multiple abscesses when larger ones are treated surgically.

- WBC/ESR may be normal, blood cultures rarely helpful, and LP contraindicated if large mass
- CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

Treatment
- aspiration ± excision and send for Gram stain, acid-fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin (6-8 wk therapy)
  - revise antibiotics when C&S known
- anticonvulsants (1-2 yr)
- follow-up is done clinically and with MRI

Prognosis
- ~10% mortality with appropriate therapy, permanent deficits in ~50% of cases

Table 13. Stages of Cerebral Inflammation/Infection

Stage	CT Features	MRI Features	Microstructural changes
Early cerebritis (1-3 d)	Low attenuation abnormality Mass effect	Low T1 signal High T2 signal Patchy contrast enhancement Increased lesion demarcation	Neutrophil accumulation Tissue necrosis and edema Microglia and astrocyte activation
Late cerebritis (4-9 d)			Macrophage and lymphocyte infiltration Microglia and astrocyte activation
Early capsule formation (10-13 d)	Ring contrast enhancement, particularly in late capsule formation	Better demarcation of lesion Ring contrast enhancement Medial growth with thinner medial wall Restricted DWI	Formation of thin, well-vascularized wall Microglia and astrocyte activation
Late capsule formation (≥ 14 d)			Thick capsule with multiple layers Microglia and astrocyte activation

Blood

Table 14. Comparison of Epidemiology and Etiology of Intracranial Bleeds

Types of Hematoma/ Hemorrhage	Etiology	Epidemiology	Clinical Features	CT Features	Treatment	Prognosis
Epidural Hematoma	Skull fracture causing middle meningeal bleed	M>F (4:1), associated with trauma	Lucid interval before loss of consciousness	Hyperdense lenticular mass with sharp margins, usually limited by suture lines	Craniotomy	Good with prompt management; respiratory arrest can occur from uncal herniation; 89% recovery at 6 mo
Acute SDH	Ruptured subarachnoid bridging vessels	Age >50, associated with trauma	No lucid interval, hemiparesis, pupillary changes	Hyperdense crescentic mass, crossing suture lines	Craniotomy if bleed >1 cm thick	40-60% mortality in patients requiring surgery
Chronic SDH	Ruptured subarachnoid bridging vessels	Age >50, EtOH users, anticoagulated	Often asymptomatic, minor H/A, confusion, signs of increased ICP, light-headedness	Hypodense crescentic mass, crossing suture lines	Burr hole to drain; craniotomy if recurs	8.6% mortality at 6 mo with drain, 18.1% without
SAH	Trauma, spontaneous (aneurysms, idio-pathic, AVM)	Age 55-60, 20% cases under age 45	Sudden onset thunderclap H/A, signs of increased ICP	Hyperdense blood in cisterns/fissures (sensitivity decreases over time)	Nonsurgical: NPO, IV normal saline (NS), ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed; external ventricular drainage or internal CSF diversion may be needed if secondary hydrocephalus	Traumatic: 0.6% mortality with isolated SAH in the setting of mild traumatic brain injury (GCS >13) More severe TBI is typically associated with additional forms of brain injury. Aneurysmal: 50% mortality at 1 mo 20-40% with moderate to severe disability with treatment
ICH	HTN, vascular abnormality, tumours, infections, coagulopathy	Age >55, male, drug use (cocaine, EtOH, amphetamine)	TIA-like symptoms, signs of increased ICP	Hyperdense intra-parenchymal collection	Medical: decrease BP, control ICP Surgical: craniotomy	Poor: 44% mortality due to cerebral herniation

CT Density and MRI Appearance of Blood

Time	CT	MRI T1	MRI T2
Acute (<72 h)	Hyper-dense	Grey	Black
Subacute (<3 wk)	Isodense	White	White
Chronic (>3 wk)	Hypo-dense	Black	Black

MRI-T1: "**G**eorge **W**ashington **B**ridge"
MRI-T2: "Oreo" cookie – **B**lack/**W**hite/**B**lack

Epidural (Extradural) Hematoma

Etiology
- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, diploic veins, dural sinus, or bone

Epidemiology
- young adult, M:F=4:1; rare in ages <2 or >60
- 1-4% of traumatic head injuries

Clinical Features
- classic sequence (seen in <30%): post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, aphasia, seizures, HTN, and respiratory distress
- deterioration can take hours to days

Investigations
- CT without contrast: "lenticular-shaped," usually limited by suture lines but not limited by dural attachments (not visible on initial CT in 8% of cases)

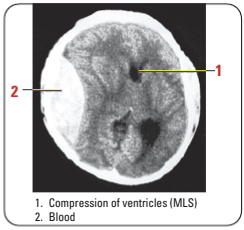
Treatment
- admission, close neurological observation with serial CT indicated if all of the following are present
  - small volume clot (<30 mL), clot thickness <15 mm, minimal midline shift (MLS <5 mm), GCS >8, no focal deficit
- otherwise, urgent craniotomy to evacuate clot, follow-up CT
- patients with initial epidural hematoma >10 mL on CT within 2 h or epidural hematoma enlargement in temporoparietal region are more likely to develop epidural hematoma enlargement and require close CT follow-up at 5-6 h post impact
- mannitol preoperative if elevated ICP or signs of brain herniation
- reverse anticoagulation if on warfarin

Prognosis
- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration preoperatively
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)

Subdural Hematoma

Table 15. Comparison of Epidemiology and Etiology of Acute and Chronic SDH

	Acute SDH	Chronic SDH
Time Course	1-2 d after bleeding onset	≥15 d after bleeding onset
Etiology	Rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration	May start out as acute SDH Often due to minor injuries or no history of injury Blood within the subdural space evokes an inflammatory response: Fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot (forming a hygroma) Course is determined by the balance of rebleeding from neomembranes and resorption of fluid
Risk Factors	Trauma, acceleration-deceleration injury, anticoagulants, EtOH, cerebral atrophy, infant head trauma, shaken baby syndrome	Advanced age, alcoholics, patients with CSF shunts, anticoagulants, coagulopathies, shaken baby syndrome
Clinical Features	Altered LOC, pupillary irregularity, hemiparesis Up to 50% of patients can present with coma from the time of injury	May present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ± seizures, progressive dementia, gait problem, light-headedness Presents with global rather than focal deficits, such as disturbance of consciousness; "the great imitator" of dementia, tumours
Investigations	CT: hyperdense, concave, crescentic mass, crossing suture lines	CT: hypodense (liquefied clot), crescentic mass
Treatment	Indications for craniotomy: if clinically symptomatic, hematoma >1 cm thick, MLS >5 mm, GCS decreased by >2 from time of injury to hospital admission, or ICP persistently >20 mmHg (optimal if surgery <4 h from onset) Otherwise observe with serial imaging if stable or improving	Seizure prophylaxis only if post-traumatic seizure Reverse coagulopathies Burr hole drainage of liquefied clot indicated if symptomatic or thickness >1 cm; craniotomy if recurs more than twice
Prognosis	Poor overall since the brain parenchyma is often injured (mortality range is 50-90%, due largely to underlying brain injury) Prognostic factors: initial GCS and neurological status, postoperative ICP	Good overall as brain usually undamaged, but may require repeat drainage



1. Compression of ventricles (MLS)
2. Blood

Figure 18. Extradural hematoma on CT

Poor Prognostic Indicators for Epidural Hematoma
- Older age
- Low GCS on admission
- Pupillary abnormalities (especially non-reactive)
- Longer delay in obtaining surgery (if needed)
- Postoperative elevated ICP

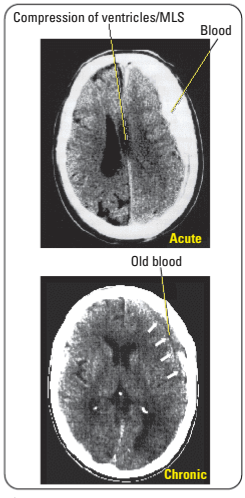


Figure 19. Subdural hematoma on CT

Use of Drains vs. No Drains After Burr-Hole Evacuation For Treatment of Chronic Subdural Hematoma
Cochrane DB Syst Rev 2016;(8):CD011402
Purpose: To compare external subdural drains to no drains after burr-hole evacuation for treatment of chronic SDH.
Methods: Systematic review with comprehensive search strategy databases extracting 9 RCTs (n=968).
Results: Significant reduction in the risk of recurrence with subdural drains (RR 0.45, 95% CI 0.32-0.61), no strong evidence of increase in complications (RR 0.78, 95% CI 0.77-1.72), mortality (RR 0.78, 95% CI 0.45-1.33), poor functional outcome (RR 0.68, 95% CI 0.44-1.05).
Conclusions
1. Some evidence that postoperative drainage is effective in reducing the symptomatic recurrence of chronic subdural hematoma.
2. The effect of drainage on the occurrence of surgical complications, mortality, and poor functional outcomes is uncertain due to low quality evidence.
3. No strong evidence of increase in complications when drains are used.

Cerebrovascular Disease

Cerebrovascular disease may be divided into two general categories:

Ischemic Cerebral Infarction (80% of disease)
- includes embolism, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc. (see Neurology, *Stroke*, N51)

Intracranial Hemorrhage (20% of disease)
- includes SAH, spontaneous ICH, IVH
- may occur due to ruptured intracranial aneurysms

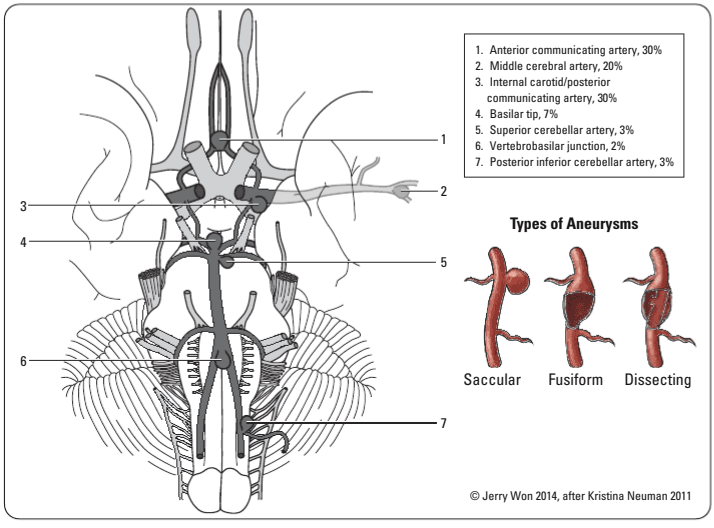


Figure 20. Aneurysms of the Circle of Willis: figure outlines most common aneurysms in the vessels

Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke
NEJM 2014;370:1091-1100
Purpose: To determine if early decompressive hemicraniectomy reduces mortality among patients >60 yr.
Methods: 112 patients >60 yr (median age 70 yr) with malignant MCA infarction randomly assigned to conservative ICU treatment vs. hemicraniectomy. Endpoint was survival without severe disability (modified Rankin scale score 0-4).
Results: The proportion of patients who survived without severe disability was 38% in the hemicraniectomy group and 18% in the control group (OR 2.91, 95% CI 1.06-7.49). Modified Rankin scale scores in hemicraniectomy vs. control group in terms of percentages of patients: 0-2 (0% vs. 0%), 3 or moderate disability (7% vs. 3%), 4 or moderate severe disability (32% vs. 15%), 5 or severe disability (28% vs. 13%), and 6 or death (33% vs. 70%). Infections were more frequent in the hemicraniectomy group and herniation more frequent in the control group.
Conclusions: Hemicraniectomy increased survival without severe disability among patients >60 yr with a malignant MCA infarction.

Subarachnoid Hemorrhage

Definition
- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

Etiology
- trauma (most common)
- spontaneous
  - ruptured aneurysms (75-80%)
  - idiopathic (14-22%)
  - AVMs (4-5%)
- coagulopathies (iatrogenic or primary), vasculitides, tumours, cerebral artery dissections (<5%)

Epidemiology
- ~10-28 in 100000 per yr
- peak age 55-60, 20% of cases occur <45 yr

Risk Factors
- HTN
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance use disorder (cigarette smoking, cocaine, EtOH)
- conditions associated with high incidence of aneurysms (see *Intracranial Aneurysms, NS24*)

Clinical Features of Spontaneous SAH
- sudden onset (seconds) of severe "thunderclap" H/A usually following exertion and described as the "worst headache of my life" (up to 97% sensitive, 12-25% specific)
- N/V, photophobia
- meningismus (neck pain/stiffness, positive Kernig's and Brudzinski's sign)

Hunt and Hess Grade (Clinical Grading Scale for SAH)

Grade	Description
1	No Sx or mild H/A and/or mild meningismus
2	Grade 1 + CN palsy
3	Confusion/lethargy, mild hemiparesis, or aphasia
4	GCS <15 but >8, moderate-severe hemiparesis, mild rigidity
5	Coma (GCS <9), decerebrate, moribund appearance

Mortality of Grade 1-2 20%, increased with grade

- decreased LOC (due to either raised ICP, ischemia, or seizure)
- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
- reactive HTN
- sentinel bleeds
  - represents undiagnosed SAH
  - SAH-like symptoms lasting <1 d ("thunderclap H/A")
  - may have blood on CT or LP
  - ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
- DDx: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

Investigations

- non-contrast CT (NCCT) for diagnosis of SAH
  - 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  - may be negative if small bleed or presentation delayed several days
  - acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
- LP (highly sensitive) for diagnosis of SAH if CT negative but high suspicion:
  - elevated opening pressure (>18 cm H_2O)
  - bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12 h, lasts 2 wk
  - RBC count usually >100000/mm^3 without significant drop from first to last tube (in contrast to traumatic tap)
  - elevated protein due to blood breakdown products
- four vessel cerebral angiography ("gold standard" for aneurysms)
  - demonstrates source of SAH in 80-85% of cases
  - angiogram negative SAH: repeat angiogram in 7-14 d, if negative → "perimesencephalic SAH"
- MRA and CT angiography/angiogram (CTA): sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

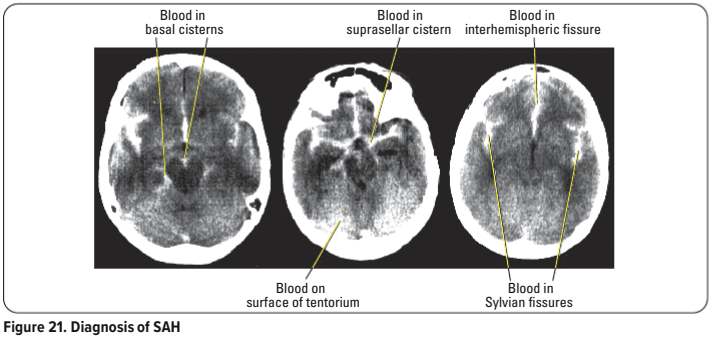

Blood in basal cisterns
Blood in suprasellar cistern
Blood in interhemispheric fissure
Blood on surface of tentorium
Blood in Sylvian fissures

Figure 21. Diagnosis of SAH

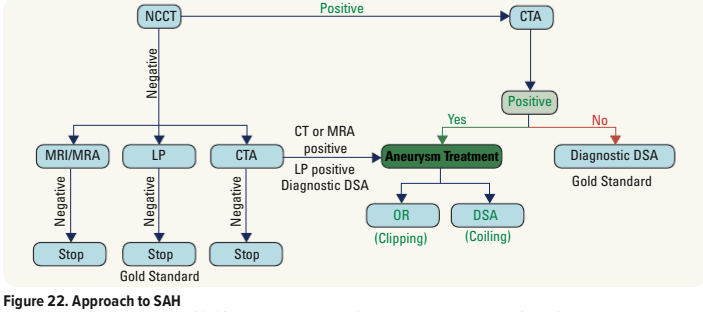


Figure 22. Approach to SAH

Adapted from: de Oliveira Manoel et al. (2014) Subarachnoid haemorrhage from a neuroimaging perspective. Critical Care

Treatment

- admit to ICU or NICU
  - oxygen/ventilation PRN
  - NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1 h
  - aim to maintain sBP=120-150 mmHg (balance of vasospasm prophylaxis, risk of rebleed, risk of hypotension since CBF autoregulation impaired by SAH)
  - cardiac rhythm monitor, Foley PRN, strict monitoring of ins and outs

World Federation of Neurological Surgeons (WFNS) Grading of SAH

WFNS Grade	GCS Score	Aphasia, Hemiparesis, or Hemiplegia
0 *		
1	15	–
2	13-14	–
3	13-14	+
4	7-12	+ or –
5	3-6	+ or –

*Intact aneurysm

Nontraumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule
Ann Emerg Med 2013;61(1):1-10
Purpose: To validate two decision rules for the diagnosis of SAH: (1) A clinical prediction rule states that patients with acute severe H/A but without the clinical variables age ≥40 yr, neck pain, loss of consciousness, or onset of H/A with exertion are at low-risk for SAH; (2) An imaging prediction rule bases diagnosis on non-contrast cranial CT for patients within 6 h of H/A onset.
Methods: Matched case-control study of 55 patients at 21 emergency departments between 2000 and 2011, and diagnoses were verified by LP.
Results: The clinical prediction rule for diagnosis of SAH was 97.1% sensitive, 22.7% specific, and had a negative likelihood ratio of 0.13. Using the imaging prediction rule resulted in a false negative rate of 20%.
Conclusions: Performing the clinical and imaging rules together has the potential for maximizing sensitivity of prediction and reducing rates of LP, but using imaging alone can result in missed cases.

The Vasograde: A Simple Grading Scale for Prediction of Delayed Cerebral Ischemia after Subarachnoid Hemorrhage
Stroke 2015;46(7):1826-1831
Purpose: Patients are classically at risk of DCI after aneurysmal SAH. This study validated a grading scale – the VASOGRADE – for prediction of DCI.
Methods: Data from three Phase II RCTs and a single hospital series were used to assess the relationship between the VASOGRADE and DCI.
Results: In a cohort of 746 patients, the VASOGRADE significantly predicted DCI (P<0.001). The VASOGRADE-Yellow had a tendency for increased risk for DCI (OR 1.31; 95% CI 0.77-2.23) when compared with VASOGRADE- Green; those with VASOGRADE-Red had a 3-fold higher risk of DCI (OR 3.19; 95% CI 2.07-4.50). VASOGRADE had an adequate discrimination for prediction of DCI (area under the receiver operating characteristics curve=0.63) and good calibration.
Conclusions: The VASOGRADE results validated previously published risk charts in a large and diverse sample of SAH patients, which allows DCI risk stratification on presentation after SAH. It could help to select patients at high-risk of DCI and standardize treatment protocols and research studies.

- medications
  - IV normal saline with 20 mmol KCl/L at 125-150 cc/h
  - nimodipine 60 mg PO/NG q4 h x 21 d for delayed cerebral ischemia (DCI) neuroprotection; may discontinue earlier if patient is clinically well
  - seizure prophylaxis: levetiracetam (Keppra®) 500 mg PO/IV q12 h x 1 wk
  - mild sedation PRN
  - neuroprotection
    - nimodipine: the only validated neuroprotective agent
    - IV magnesium and clazosentan (endothelium-A receptor antagonist): studies show reduction in DCI and vasospasm, respectively, without any effect on functional outcome
    - statins: trial did not show any neuroprotective benefit

Complications

- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood can lead to delayed cerebral ischemia and death
  - onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
  - clinical features (new onset ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor, e.g. pronator drift)
  - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
  - "symptomatic" vasospasm in 20-30% of SAH patients
  - "angiographic" vasospasm in 30-70% of arteriograms performed 7 d following SAH
  - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
  - risk of cerebral infarct and death
  - treatment
    - hyperdynamic ("triple H") therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
    - direct vasodilation via angioplasty or intra-arterial verapamil for refractory cases
- delayed cerebral ischemia: neurological deterioration persisting >1 h in the absence of any obvious contributing physiological, radiological, or laboratory abnormalities
  - peaks 4-10 d post-ictus
  - can progress to cerebral infarction and is associated with significant morbidity and mortality
  - mechanism behind DCI is unclear, but includes vasospasm, vascular dysautoregulation, neurotoxic effects from the blood breakdown products, inflammation, micro-thrombi, and cortical spreading depolarizations
  - essential target for SAH management
- hydrocephalus (15-20%): due to blood obstructing arachnoid granulations
  - can be acute or chronic, requires extraventricular drain or shunt, respectively
- neurogenic pulmonary edema
- hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECF volume loss), not SIADH
- DI
- cardiac: arrhythmia (>50% have ECG changes), MI, CHF

Prognosis

- 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
- 30% of survivors have moderate to severe disability
- a major cause of mortality is rebleeding, for untreated aneurysms:
  - risk of rebleed: 4% on 1st day, 15-20% within 2 wk, 50% by 6 mo
  - if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  - only prevention is early clipping or coiling of "cold" aneurysm
  - rebleed risk for "perimesencephalic SAH" is approximately same as for general population

Intracranial Aneurysms

Epidemiology

- prevalence 1-4% (20-30% have multiple)
- F>M; 35-65 yr (mean age of presentation is 50 yr)

Types

- saccular (berry)
  - most common type
  - located at branch points of major cerebral arteries (circle of Willis)
  - 85-95% in carotid (anterior) system, 5-15% in vertebrobasilar (posterior) circulation
- fusiform
  - atherosclerotic
  - more common in vertebrobasilar system, rarely rupture
- infectious (mycotic)
  - secondary to any infection of vessel wall, 20% multiple
  - 60% *Streptococcus* and *Staphylococcus*
  - 3-15% of patients with bacterial endocarditis

VASOGRADE

VASOGRADE	WFNS	Modified Fisher scale
Green	1-2	1-2
Yellow	1-3	3-4
Red	4-5	Any

The Durability of Endovascular Coiling vs. Neurosurgical Clipping of Ruptured Cerebral Aneurysms: 18 Yr Follow-Up of The UK Cohort of The International Subarachnoid Aneurysm Trial (ISAT)

Lancet 2015;385(9969):691-697

Methods: RCT comparing endovascular coiling treatment with craniotomy and clipping for ruptured intracranial aneurysms in 2143 patients who were considered eligible for either modality or therapy between 1994-2002. 1644 patients were followed for deaths and outcomes for 10-18.5 yr.

Results: At 10 yr, 83% of endovascular coiling group and 79% of neurosurgical clipping group were alive. 82% of patients treated with endovascular coiling and 78% of patients treated with neurosurgical clipping were independent. Patients in the endovascular group were more likely to be alive and independent at 10 yr vs. neurosurgery group (OR 1.34, 95% CI 1.07-1.67). Rebleeding risks from target aneurysm for endovascular group and neurosurgery group were 0.0216 (95% CI 0.0121-0.0383) and 0.0064 (95% CI 0.0024-0.0173), respectively.

Conclusions:

1. The probability of death or dependency was significantly greater in the neurosurgical group (vs. endovascular group) at 10 yr follow-up.
2. Rebleeding was more likely in endovascular group (vs. neurosurgical group), but risk was small at 10 yr follow-up.
3. Probability of disability-free survival was significantly greater in the endovascular group (vs. neurosurgical group) at 10 yr follow-up.

Most Common Locations of Saccular Aneurysms

- Anterior communicating artery (ACom): 30%
- PCom: 25%
- MCA: 20%
- Basilar tip: 7%

Risk Factors for Saccular Aneurysms

Smoking
HTN
Adult Polycystic kidney disease
Ehlers-Danlos syndrome
Family history: ≥2 first-degree relatives

Risk Factors
- autosomal dominant polycystic kidney disease (15%)
- fibromuscular dysplasia (7-21%)
- AVMs
- connective tissue diseases (Ehlers-Danlos syndrome, Marfan syndrome)
- family history
- bacterial endocarditis
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- atherosclerosis, HTN, and smoking
- trauma

Table 16. Five Year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

	Cavernous Carotid	ACA or ACom/MCA/ICA	Vertebrobasilar/PCA/PCom
<7 mm	0%	0%	2.5%
7-12 mm	0%	2.6%	14.5%
13-24 mm	3%	14.5%	18.4%
≥24 mm	6.4%	40%	50%

ACA = anterior cerebral artery
Table adapted from the ISUIA Trial; Lancet 2003;362:103-110

Clinical Features
- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage ("thunderclap H/A") → requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  - ICA or ACom aneurysm may compress:
    - the pituitary stalk or hypothalamus causing hypopituitarism
    - the optic nerve or chiasm producing a visual field defect
    - basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
    - PCom aneurysm may produce CN III palsy
    - intracavernous aneurysms (CN III, IV, V1, V2, VI)
- distal embolization (e.g. amaurosis fugax)
- seizures
- H/A (without hemorrhage)
- incidental CT or angiography finding (asymptomatic)

Investigations
- CTA, MRA, cerebral angiogram

Treatment
- ruptured aneurysms
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
    - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), coiling using Guglielmi detachable coils, flow diversion stents, wrapping (last resort)
  - choice of surgery vs. coiling: consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition; in general:
    - endovascular coiling > clipping for ruptured intracranial aneurysms suitable for both treatments → greater survival benefit at 1 yr with sustained effect for up to 7 yr post-treatment
    - coiling: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    - clipping: difficult endovascular access, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- unruptured aneurysms
  - average 1.4% annual risk of rupture; predictors include: age, HTN, history of SAH, aneurysm size and location, and geographical region (Finnish people = 3.6 times increased risk; Japanese people = 2.8 times increased risk)
  - no clear evidence on when to operate; need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20-50%) vs. risk of coiling (~2%)
  - generally treat unruptured aneurysms >10 mm
  - treatment guided by balance of risks of SAH per ISUIA and PHASES and of intervention per centre experience and outcomes
  - follow smaller aneurysms with serial angiography

Long-Term, Serial Screening for Intracranial Aneurysms in Individuals with a Family History of Aneurysmal Subarachnoid Hemorrhage: A Cohort Study
Lancet Neurol 2014;13:385-392
Purpose: To examine the yield of long-term serial screening for intracranial aneurysms for individuals with a positive family history of aneurysmal subarachnoid hemorrhage (a SAH) (two or more first degree relatives who have had aSAH or unruptured intracranial aneurysms).
Study: Screening results from April 1 1993 to April 1 2013 were reviewed in a cohort study. MRA or CTA was done from ages 16-18 to ages 65-70. After a negative screen, individuals were advised to contact the clinic in 5 yr for follow-up.
Results: Aneurysms were identified in 11% of individuals at first screening (n=458), 8% at second screening (n=261), 5% at third screening (n=128), and 5% at fourth screening (n=63). Smoking (OR 2.7, 95% CI 1.2-5.9), history of previous aneurysms (3.9, 1.2-12.7), and familial history of aneurysms (3.5, 1.6-8.1) were significant risk factors for aneurysm at first screening. History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening (HR 4.5, 95% CI 1.1-18.7).
Conclusions: The benefit of long-term screening in individuals with a family history of aSAH is substantial up to and after 10 yr of follow-up and two initial negative screens.

The Unruptured Intracranial Aneurysm Treatment Score
Neurology 2015;85(10):881-889
Purpose: To develop an unruptured intracranial aneurysm (UIA) treatment score (UIATS) model that includes and quantifies key factors involved in clinical decision-making in the management of UIAs and to assess agreement for this model among specialists in UIA management and research.
Methods: An international multidisciplinary (neurosurgery, neuroradiology, neurology, clinical epidemiology) group of 69 specialists was convened to develop and validate the UIATS model using a Delphi consensus method.
Results: The UIATS accounts for 29 key factors in UIA management.
Conclusions: This novel UIA decision guidance study captures an excellent consensus among highly informed individuals on UIA management, irrespective of their underlying specialty.

See Landmark Neurosurgery Trials table for more information on the natural history of unruptured intracranial aneurysms and the risk associated with the repair.

Intracerebral Hemorrhage

Definition
- hemorrhage within brain parenchyma, accounts for ~10% of strokes
- can dissect into ventricular system (IVH) or through cortical surface (SAH)

Etiology
- HTN (usually causes bleeds at putamen, thalamus, pons, and cerebellum)
- hemorrhagic transformation (reperfusion post-stroke, surgery, strenuous exercise, etc.)
- vascular anomalies
  - aneurysm, AVMs, and other vascular malformations (see *Vascular Malformations, NS27*)
  - venous sinus thrombosis
  - arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
- tumours (1%): often malignant (e.g. GBM, lymphoma, metastases)
- drugs (amphetamines, cocaine, alcohol, anticoagulants, etc.)
- coagulopathy (iatrogenic, leukemia, thrombotic thrombocytopenic purpura, aplastic anemia)
- CNS infections (fungal, granulomas, herpes simplex encephalitis)
- post-trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
- eclampsia
- postoperative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
- idiopathic

Epidemiology
- 12-31 in 100000 per yr

Risk Factors
- increasing age (mainly >55 yr)
- male
- HTN
- Black/Asian > White
- previous cerebrovascular accident of any type (23 times risk)
- both acute and chronic heavy EtOH use; cocaine, amphetamines
- liver disease
- anticoagulants

Clinical Features
- TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
- gradual onset of symptoms over min-hr, usually during activity
- H/A, N/V, and decreased LOC are common
- specific symptoms/deficits depend on location of ICH

Investigations
- baseline severity score such as the ICH Score should be performed as part of the initial workup
- hyperdense blood on non-contrast CT
- CTA routine, if spot sign (contrast in the hematoma) demonstrated there is high likelihood of clot growth

Treatment
- patients should be transferred to and managed in a neuro-ICU or stroke unit
- medical
  - decrease MAP to pre-morbid level or by ~20% (target BP 140/90 mmHg) in emergency department
  - check partial thromboplastin time/international normalized ratio (PTT/INR), and correct coagulopathy (immediate reversal of anticoagulation)
  - control raised ICP (see *Intracranial Pressure Dynamics, NS4*)
  - corticosteroids should NOT be used for elevated ICP in ICH
  - levetiracetam/phenytoin for seizure prophylaxis
  - follow electrolytes (SIADH common)
  - angiogram to rule out vascular lesion unless >45 yr, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~0%)
- surgical
  - craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
  - indications
    - symptoms of raised ICP or mass effect
    - rapid deterioration (especially if signs of brainstem compression)
    - favourable location (e.g. cerebellar, non-dominant hemisphere)
    - young patient (<50 yr)
    - suspected tumour, AVM, aneurysm, or cavernoma (resection or clip to decrease risk of rebleed)
  - contraindications
    - small bleed: minimal symptoms, GCS >10
    - poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function

Location of ICH
- Basal ganglia/internal capsule (50%)
- Thalamus (15%)
- Cerebral white matter (15%)
- Cerebellum/brainstem – usually pons (15%)
- Other (5%)

ICH Score Components
- GCS score (3-4=2 pts; 5-12=1 pt, 13-15=0 pt)
- ICH volume (≥30 cm=1 pt, <30 cm=0 pt)
- Presence of IVH (yes=1 pt, no=0 pt)
- Infratentorial origin (yes=1 pt, no=0 pt)
- Age (≥80 =1 pt, <80 =0 pt)

Surgical Decision Making in Brain Hemorrhage: New Analysis of the STICH, STICH II and STITCH (Trauma) Randomized Trials
Stroke 2019;50:1108-1115
Summary: The STICH (Surgical Trial in Lobar Intracerebral Hemorrhage) I (n=1033 patients) and II (n=601 patients) trials randomized patients with spontaneous intracerebral hemorrhage (ICH) to early surgery or initially conservative treatment. The STITCH (Trauma) trial investigated these options in the context of head-injured patients (n=170 patients). Meta-analysis of spontaneous ICH patients suggests that those presenting with a GCS of 10-13 and a large ICH are more likely to benefit from early surgery than those presenting with a GCS outside this range. Surgical treatment of traumatic ICH with GCS 10-13 may have similarly beneficial outcomes.
Refer to the Landmark Neurosurgery Trials table for details of STICH.

Spetzler-Martin AVM Grading Scale

Item	Score
Size	
0-3 cm	1
3.1-6.0 cm	2
>6 cm	3
Location	
Non-eloquent	0
Eloquent	1
Deep Venous Drainage	
Not present	0
Present	1

AVM grades are calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table.
e.g. a 2 cm tumour in non-eloquent location without deep venous drainage = Grade I

- medical reasons (e.g. advanced age, severe coagulopathy, difficult location (e.g. basal ganglia, thalamus))

Prognosis
- 30 d mortality rate 44%, mostly due to cerebral herniation
- rebleed rate 2-6%, higher if HTN poorly controlled

Vascular Malformations

Types
- AVMs
- cavernous malformations (cavernomas, cavernous hemangiomas/angiomas)
- venous angioma
- capillary telangiectasias
- AVF (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- "angiographically occult vascular malformations" (any type, 10% of malformations)

Arteriovenous Malformations, Cavernous Malformations, and Dural Arteriovenous Fistulas

Table 17. Comparison of Pathoetiology, Clinical Features, and Treatment of Arteriovenous Malformations, Cavernous Malformations, and Dural Fistulas

	Arteriovenous Malformations	Cavernous Malformations	Dural Fistulas
Definition	Tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma; usually congenital	Benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins Several genes now described: *CCM1, CCM2, CCM3*	Fistulas connecting dural arteries to dural veins or the dural sinus Frequently occur at the transverse and cavernous sinuses, but can be found at every cranial dural sinus Hypothesized to be related to venous sinus thrombosis formation, and subsequent microvascular shunt formation within the dura between arteries and veins
Epidemiology	Prevalence ≈0.14%, M:F=2:1, average age at diagnosis=33 yr 15-20% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs	Prevalence of 0.1-0.2%, both sporadic and hereditary forms described	Unknown true incidence Constitute 10-15% of all intracranial vascular abnormalities
Clinical Features	Hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections Seizures (50%): more common with larger AVMs Mass effect Focal neurological signs secondary to ischemia (high flow → "steal phenomena") Localized H/A, increased ICP Bruit (especially with dural AVMs) May be asymptomatic ("silent")	Seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A Often an incidental finding Hemorrhage risk less than AVM, usually minor bleeds	Asymptomatic, pulsatile tinnitus if involving sigmoid or transverse sinuses, bruits, H/A Carotid cavernous involvement classically produces proptosis, chemosis, and bruits Symptoms of SAH, SDH, or ICH
Investigations	MRI (flow void), MRA Angiography (7% will also have one or more associated aneurysms)	T2-weighted image MRI (non-enhancing) Gradient echo sequencing (best for diagnosis)	Angiography remains the gold standard Non-enhanced CT to rule out hemorrhage MRI; however, this does not demonstrate the arterial supply to the fistula
Treatment	Decreases risk of future hemorrhage and seizure Surgical excision is treatment of choice even in Spetzler-Martin grades I – II with general good health SRS is preferred for small (<3 cm) or very deep lesions Endovascular embolization (glue, balloon) can be curative (5%) or used as adjuvant to surgery or SRS in larger lesions Conservative (e.g. palliative embolization, seizure control if necessary)	Surgical excision: Only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions)	Approach is dependent on size, location and symptoms, and includes: Conservative treatment Neuroradiological endovascular interventions Radiation therapy Surgery Combination of the above
Prognosis	12-66% mortality, 23-40% morbidity (serious neurological deficit) per bleed Risk of major bleed in untreated AVMs: 2-4%/yr Outcomes depend on Spetzler-Martin grade	Annual bleeding rates: 0.25-1.1% for supratentorial, 2-3% for brainstem Symptomatic lesions have a higher hemorrhage risk than asymptomatic	0.1% annual risk of hemorrhage 6.9% annual risk for non-hemorrhagic neurological deficit 10.4% mortality rate Outcomes influenced by dural fistula type (presence of cortical venous drainage → poorer outcomes)

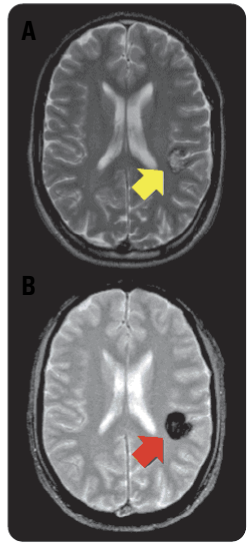


Figure 23. MRI of cavernous malformation
A. T2-weighted imaging MRI
B. Gradient echo sequencing MRI

Clinical Course of Untreated Cerebral Cavernous Malformations (CCM)
Lancet Neurol 2015 pii:S1474-4422(15)00303-8
Purpose: To obtain precise estimates and predictors of the risk of intracranial hemorrhage (ICH) in patients with untreated cerebral cavernous malformations (CCMs).
Methods: Collected individual patient data from investigators of published studies on MEDLINE and Embase since inception until April 2015 (7 cohorts from 6 studies, n=1620) on clinical course from CCM diagnosis until first CCM treatment or last available follow-up.
Results: course from CCM diagnosis until first CCM treatment or last available follow-up.
Results: 204 of the 1620 patients experienced ICH during 5187 person-yr follow-up (Kaplan-Meier estimated 5 yr risk 15.8%, 95% CI 13.7-17.9). ICH within 5 yr of CCM diagnosis was associated with clinical presentation with ICH or focal neurological deficit without brain imaging evidence of recent hemorrhage (vs. other presentations; HR 5.6, 95% CI 3.2-9.7) and with brainstem CCM location (vs. other locations; HR 4.4, 95% CI 2.3-8.6).
Conclusions: (1) Mode of clinical presentation and (2) CCM location are independently associated with ICH within 5 yr of CCM diagnosis. The risk of recurrent hemorrhage from a CCM is greater than the risk of the first event and declines over 5 yr.

Cerebrospinal Fluid Fistulas

Etiology
- cranial or spinal
- traumatic: after head trauma, iatrogenic (post transsphenoidal surgery, post skull base surgery)
- nontraumatic: high pressure (hydrocephalus, tumour), normal pressure (bone erosion secondary to infection, congenital defect)

Clinical Features
- otorrhea or rhinorrhea (clear fluid)
- low pressure H/A (worse when sitting up)
- confirmatory testing for CSF: β-transferrin test, quantitative glucose analysis of fluid, "ring sign," "reservoir sign"

Investigations
- CT (detect pneumocephalus, fractures, skull base defects), water contrast CT cisternography

Treatment
- lower ICP (avoid straining, acetazolamide to reduce CSF production, modest fluid restriction)
- persistent leak: may require continuous lumbar drainage via percutaneous catheter
- surgical indications: traumatic leak lasting >2 wk, spontaneous leaks, delayed onset of leak after trauma or surgery, leaks complicated by meningitis

Suspect CSF fistula in patients with otorrhea or rhinorrhea after head trauma or recurrent meningitis

Ring Sign: Demonstrates if CSF is mixed with blood. Allow CSF to drain onto the surrounding sheets; positive if clear in centre with surrounding blood coloured ring (double ring sign)
Reservoir Sign: Gush of CSF leaks out in certain head positions (i.e. teapot sign); not specific or sensitive

Red Flags for Back Pain

BACK PAIN
Bowel/Bladder (retention or incontinence)
Anesthesia (saddle)
Constitutional symptoms
"K"hronic disease
Paresthesia
Age >50 or <20
IV drug use
Neuromotor deficits

Cauda Equina
Urinary retention or incontinence, fecal incontinence or loss of anal sphincter tone, saddle anesthesia, uni/bilateral leg weakness/pain
Malignancy
Age >50, previous Hx of cancer, pain unrelieved by bed rest, constitutional symptoms
Infection
Increased ESR, IV drug use, immunosuppressed, fever
Compression Fracture
Age >50, trauma, prolonged steroid use

EXTRACRANIAL PATHOLOGY

Approach to Limb/Back Pain

- see Orthopedic Surgery

Extradural Lesions

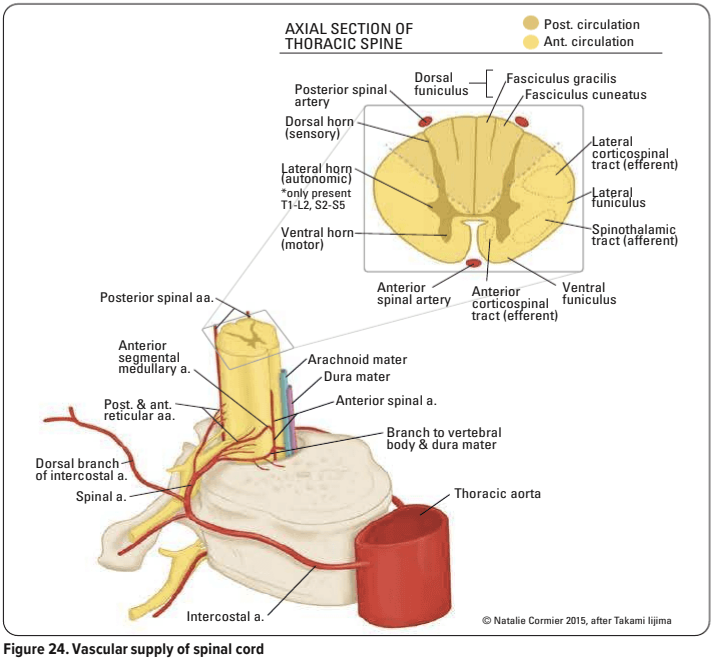


Figure 24. Vascular supply of spinal cord

Root Compression

- radiculopathy is a pain and/or sensorimotor deficit syndrome that involves compression of a nerve root. Nerve compression generally occurs as a result of disc herniation, degenerative disc diseases (spondylosis), instability, and masses (rare)
- patients generally present with referred pain, sensory changes (numbness and/or tingling) or weakness. Whereas patients might sometimes describe sensory changes in a dermatomal distribution, the referred pain will not be in a dermatomal distribution. The areas of pain and altered sensorium may be incongruent
- muscle innervation has less overlap than sensory innervation and hence is a better predictor of level of pathology

Sensory Fibres
- Fasciculus gracilis/cuneatus: proprioception, fine touch, vibration
- Spinothalamic tract: pain and temperature

Motor Fibres
- Corticospinal tract: skilled movements

Differential Diagnosis

- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

Cervical Disc Syndrome

Etiology

- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C5-C6 (C6 root) and C6-C7 (C7 root)
- cervical spondylosis can lead to nerve root compression due to foraminal compression)

Disc herniations impinge the nerve root at the level **below** the interspace (i.e. C5-6 disc affects the C6 nerve root)

Clinical Features

- pain in arm follows nerve root distribution, worse with neck extension, ipsilateral rotation, and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms (diminished reflexes, non-spastic motor weakness)
- central cervical disc protrusion and/or cervical spondylosis with osteophytes may cause myelopathy as well as nerve root deficits

Investigations

- if red flags (e.g. symptoms/signs of myelopathy; motor deficits; night pains): cervical spine (C-spine) x-ray, CT, MRI (imaging of choice)
- only consider EMG/nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue

Treatment

- nonsurgical
  - no bed rest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics; NSAIDs are more efficacious
- avoid cervical manipulation
- surgical indications
  - anterior cervical discectomy and fusion is the usual approach (posterior foraminotomy with discectomy is another option; cervical artificial disc is an emerging option)
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurological deficit

Prognosis

- 95% improve spontaneously in 4-8 wk

Table 18. Lateral Cervical Disc Syndromes

	C4-5	C5-6	C6-7	C7-T1
Root Involved	C5	C6	C7	C8
Incidence	2%	19%	69%	10%
Sensory	Shoulder	Thumb	Middle finger	Ring finger, 5th finger
Motor	Deltoid, biceps, supraspinatus	Biceps, wrist extensors	Triceps	Digital flexors, intrinsics
Reflex	No change	Biceps, brachioradialis	Triceps	Finger jerk (Hoffmann's sign)

Degenerative Cervical Myelopathy

Definition
- progressive degenerative process of cervical spine leading to canal stenosis, congenital spinal stenosis, degeneration of intervertebral discs, hypertrophy of dura or ligaments, subluxation, altered mobility, telescoping of the spine due to loss of height of vertebral bodies, alteration of normal lordotic curvature
- resultant syndromes: mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression)

Epidemiology
- typically begins at age 40-50, M>F, most commonly at the C5-C6 > C6-C7 levels

Pathogenesis
- any of: disc degeneration/herniation, osteophyte formation, ossification of the PLL, and/or hypertrophy of ligaments
- pathophysiology includes static compression, dynamic compression, and vascular compromise

Clinical Features
- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force, e.g. Spurling's test)
- the earliest symptoms are gait disturbance and lower extremity weakness or stiffness
- occipital H/A can be an accompanying feature
- radiculopathy may involve one or more roots, and symptoms include neck, shoulder, and arm pain; paresthesias; and numbness
- degenerative cervical myelopathy (DCM) may present with:
  - weakness (upper > lower extremity), lower extremity weakness (corticospinal tracts) is most worrisome complaint
  - decreased dexterity, loss of fine motor control
  - sensory changes
  - UMN findings such as hyperreflexia, clonus, and Babinski reflex
  - funicular pain, characterized by burning and stinging ± Lhermitte's sign (lightning-like sensation down the back with neck flexion)

Investigations
- x-ray of cervical spine ± flexion/extension (alignment, fractures)
- MRI most useful for determination of compression of the neural element
- CT is used for better determination of bony anatomy (i.e. OPLL)
- EMG/nerve conduction studies reserved for peripheral nerve investigation

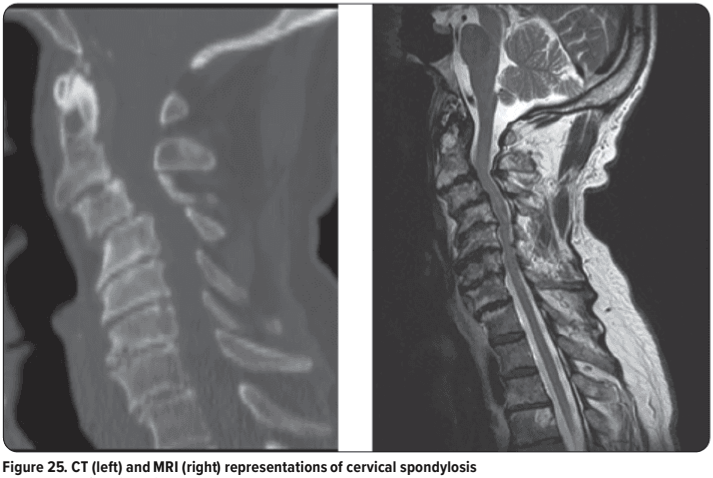


Figure 25. CT (left) and MRI (right) representations of cervical spondylosis
Images courtesy of Dr. Eric Massicotte

Treatment
- nonsurgical: physiotherapy, anti-inflammatory medications
- surgical: anterior approach (anterior cervical discectomy or corpectomy), posterior approach (decompressive cervical laminectomy)
- in multilevel DCM, both anterior and posterior options are acceptable approaches with generally comparable outcomes
  - with kyphosis → anterior approach generally preferred
  - with preserved cervical lordosis → posterior approach generally preferred

DCM is the most common cause of spinal cord impairment

Clinical Grading Scores to Assess DCM
Modified Japanese Orthopaedic Association (mJOA)
Nurick Grade
Neck Disability Index

A Clinical Practice Guideline for the Management of Patients with Degenerative Cervical Myelopathy: Recommendations for Patients with Mild, Moderate, and Severe Disease and Nonmyelopathic Patients with Evidence of Cord Compression
Global Spine Journal 2017;7(3S):70S-83S
Severe and moderate DCM: Moderate evidence suggesting strong recommendation of surgical intervention.
Mild DCM: Very low to low evidence suggesting offering surgical intervention or a structured rehabilitation and if non-operative management initially pursued, consider operative intervention if evidence of neurological deterioration.
Non-myelopathic patients without radiculopathy: In such patients with imaging evidence of cervical cord compression, suggestion of not offering prophylactic surgery; counsel, educate, and follow clinically.
Non-myelopathic patients with radiculopathy: Such patients with imaging evidence of cervical cord compression are at a higher risk of developing myelopathy and should be counselled. Offer surgical or nonoperative treatment with appropriate follow-up and structured rehabilitation.

- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain
- complete remission almost never occurs; surgical decompression stops progression of disease in almost all cases; 80% of patients experience neurological improvement

Table 19. 2017 Summary AO Spine-CSRS Guideline for the Management of Degenerative Cervical Myelopathy

Patient Population	Level of Recommendation	Guideline/Recommendation
Severe DCM (mJOA 0-11)	Strong	Surgical intervention is recommended
Moderate DCM (mJOA 12-14)	Strong	Surgical intervention is recommended
Mild DCM (mJOA 15-17)	Weak	Surgical intervention or structured rehabilitation is recommended; consider surgery if with neurologic deterioration or failure to improve
Non-myelopathic patients with cord compression and without radiculopathy	Weak	Prophylactic surgery is not recommended
Non-myelopathic patients with cord compression and with radiculopathy	Weak	Either surgical intervention or nonoperative treatment (close follow-up or structured rehabilitation)

Lumbar Disc Syndrome

Definition
- compression of nerve roots caused by herniation of the nucleus pulposus through the annulus fibrosus of an intervertebral disc in the lumbar spine

Etiology
- posterolaterally herniated disc compressed nerve root exiting BELOW the level of the disc or the traversing nerve root
- far lateral disc herniation compressed nerve root AT the level of the disc or the exiting nerve root
- central herniation may cause cauda equina compression or lumbar stenosis (NC)

Clinical Features
- initially back pain, then leg pain > back pain
- limited back movement (especially forward flexion) due to pain
- motor weakness, dermatomal sensory changes, decreased reflexes
- exacerbation with Valsalva; relief with flexing the knee or thigh
- nerve root tension signs
  - straight leg raise (SLR) (Lasegue's test) or crossed SLR (pain should occur at less than 60°) suggests L5, S1 root involvement
  - femoral stretch test suggests L2, L3, or L4 root involvement

Investigations
- MRI is modality of choice
- x-ray spine (only to rule out other lesions), CT (bony anatomy)
- myelogram and post-myelogram CT (only if MRI is contraindicated)

Treatment
- nonsurgical (same as cervical disc disease)
- surgical indications: same as cervical disc and cauda equina syndrome

Prognosis
- 95% improve spontaneously within 4-8 wk
- if no improvement is made with conservative treatment, then symptom relief can be achieved faster with surgery than with continuation of conservative management; however, the long-term outcome after surgery is comparable to conservative therapy
- do not follow patients with serial MRIs; clinical status is more important for guiding management

Table 20. Lateral Lumbar Disc Syndromes

	L3-4	L4-5	L5-S1
Root Involved	L4	L5	S1
Incidence	<10%	45%	45%
Pain	Femoral pattern	Sciatic pattern	Sciatic pattern
Sensory	Medial leg	Dorsal foot to hallux Lateral leg	Lateral foot
Motor	Tibialis anterior (dorsiflexion)	Extensor hallucis longus (hallux extension)	Gastrocnemius, soleus (plantar flexion)
Reflex	Patellar	Medial hamstrings	Achilles

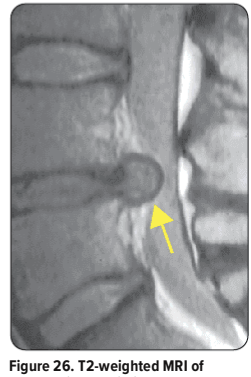


Figure 26. T2-weighted MRI of lumbar disc herniation

See Landmark Neurosurgery Trials table for more information on the SPORT trial for outcomes of surgery vs. nonoperative care for lumbar disc herniation.

Magnetic Resonance Imaging in Follow-Up Assessment of Sciatica
NEJM 2013;368:999-1007
Background: Follow-up MRI is a controversial method for monitoring sciatica in patients with known lumbar-disc herniation.
Methods: Participants (n=283) were recruited from a simultaneous, parallel, randomized study comparing surgery and conservative care for sciatica (the Sciatica Trial). MRI and clinical assessment were undertaken pre-treatment and 1 yr post-treatment randomization to visualize disc herniation and evaluate outcome.
Results: At 1 yr, disc herniation was visible in 35% with a favourable outcome (complete, or nearly complete symptom resolution) and in 33% with an unfavourable outcome (P=0.70). A favourable outcome was reported in 85% of patients with disc herniation and 83% without disc herniation (P=0.70).
Conclusions: Anatomical abnormalities visible on repeated MRI 1 yr after treatment for sciatica due to lumbar-disc herniation could not distinguish patients with resolution of their symptoms from patients still experiencing symptoms.

Table 21. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome

	Conus Medullaris Syndrome	Cauda Equina Syndrome
Onset	Sudden, bilateral	Gradual, unilateral
Spontaneous Pain	Rare, if present usually bilateral, symmetric in perineum or thighs	Severe, radicular type: in perineum, thighs, legs, back, or bladder
Sensory Deficit	Saddle; bilateral and symmetric; sensory dissociation	Saddle; no sensory dissociation; may be unilateral and asymmetric
Motor Deficit	Symmetric; paresis less marked; fasciculations may be present	Asymmetric; paresis more marked; atrophy may be present; fasciculations rare
Reflexes	Only ankle jerk absent (preserved knee jerk)	Knee and ankle jerk may be absent
Autonomic Symptoms (bladder dysfunction, impotence, etc.)	Urinary retention and atonic anal sphincter prominent early; impotence frequent	Sphincter dysfunction presents late; impotence less frequent

Cauda Equina Syndrome

Etiology
- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumour

Causes of Cauda Equina Syndrome
- Lumbar disc herniation
- Spinal stenosis
- Spinal tumour
- Epidural abscess
- Hematoma
- Trauma

Clinical Features
- usually acute (develops in <24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
  - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
  - bilateral sensory loss or pain: depends on the level affected
  - saddle area (S2-S5) anesthesia
  - sexual dysfunction (late finding)

Investigations
- urgent MRI to confirm compression of S2-S3-S4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present; volumes controversial but anything over 250 cc in a healthy individual is cause for concern

Treatment
- surgical decompression (<48 h) to preserve bowel, bladder, and sexual function, and/or to prevent progression to paraplegia
- consult radiation oncology for urgent symptomatic management if palliative oncology patient

Prognosis
- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

Lumbar Spinal Stenosis

Etiology
- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

See Landmark Neurosurgery Trials table for more information on the SPORT trial for outcomes of surgery vs. nonoperative care for symptomatic lumbar spinal stenosis.

Clinical Features
- gradually progressive back and leg pain with standing and walking relieved by sitting, lying down, or movements involving lumbar flexion (e.g. riding a bicycle, leaning over a shopping cart); NC 60% sensitive
- neurologic exam may be normal, including SLR test

Investigations
- MRI is best to confirm and localize the level of stenosis (unlike nerve root compression which can be localized with clinical exam)

Treatment
- nonsurgical: NSAIDs, analgesia, physical therapy
- surgical: laminectomy with root decompression
  - fusion typically advised if evidence of segmental instability prior to surgery (e.g. in flexion/extension x-rays)

Neurogenic Claudication

Etiology
- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

Clinical Features
- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min) and NOT simply by exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited by lumbar extension, but may not have any other neurological findings or signs of vascular compromise (e.g. ulcers, poor capillary refill)

Investigations
- bicycle test may help distinguish NC from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

Treatment
- same as for lumbar spinal stenosis

Key Features of Neurogenic vs. Vascular Claudication

Neurogenic Claudication: dermatomal distribution with positional relief occurring over minutes

Vascular Claudication: sclerotomal distribution with relief occurring with rest over seconds

Intradural Intramedullary Lesions

Syringomyelia (Syrinx)

Definition
- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over mo to yr
- initially pain, weakness; later atrophy and loss of pain and temperature sensation

Etiology
- syringomyelia can be classified as communicating or non-communicating based on the presence or absence of communication with the 4th ventricle
- most cases of communicating syringomyelia are due to Chiari malformations
- non-communicating syringomyelia arises due to localized pathology in the spinal cord that causes disruption of CSF flow dynamics (e.g. SCI, arachnoiditis)
- 70% are associated with Chiari I malformation, 10% with basilar invagination
- post-traumatic
- post-infectious
- post-inflammatory
- tumour
- tethered cord

Clinical Features
- nonspecific features for any intramedullary spinal cord pathology:
  - initially pain, weakness, atrophy, then loss of pain and temperature (spinothalamic tract) in upper extremities (central syrinx) with progressive myelopathy over years
  - sensory loss with preserved touch and proprioception (dorsal column–medial lemniscus pathway) in a band-like distribution at the level of cervical syrinx
  - dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - painless neuropathic arthropathies (Charcot's joints), especially in the shoulder and neck due to loss of pain and temperature sensation

Investigations
- MRI is best method, myelogram with delayed CT is an older option that can be considered when a MRI is not an option (e.g. pacemaker; stainless steel spine instrumentation)

Treatment
- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)
- shunting is rarely required in the setting of communicating syringomyelia associated with a Chiari I malformation; only needed when progressive and size allows for insertion of tube; shunting of a syrinx is more commonly indicated in non-communicating forms of syringomyelia (e.g. due to SCI, arachnoiditis)
  - syringosubarachnoid and syringopleural shunting are two options; if the syrinx is due to focal cord tethering (e.g. due to arachnoid webs), a detethering procedure with/without duroplasty may be indicated

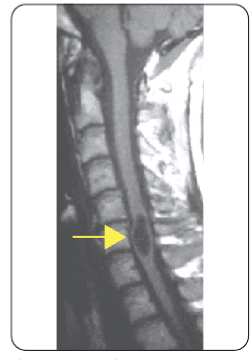


Figure 27. T1 weighted MRI of syringomyelia

Spinal Cord Syndromes

Complete Spinal Cord Lesion

- bilateral loss of motor/sensory and autonomic function at ≥4 segments below lesion/injury, with UMN signs
- about 3% of patients with complete injuries will develop some recovery within 24 h; beyond 24 h, no distal function will recover

Incomplete Spinal Cord Lesion

- any residual function at ≥4 segments below lesion
- signs include sensory/motor function in lower limbs and "sacral sparing" (perianal sensation, voluntary rectal sphincter contraction)

Table 22. Comparison Between Incomplete Spinal Cord Lesion Syndromes

Syndrome	Etiology	Motor	Sensory
Brown-Séquard	Hemisection of cord	Ipsilateral LMN weakness at the lesion Ipsilateral UMN weakness below the lesion	Ipsilateral loss of vibration and proprioception Contralateral loss of pain and temperature Preserved light touch
Anterior Cord	Anterior spinal artery compression or occlusion	Bilateral LMN weakness at the lesion Bilateral UMN weakness below the lesion Urinary retention	Preserved vibration and proprioception Bilateral loss of pain and temperature Preserved light touch
Central Cord (most common)	Syringomyelia, tumours, spinal hyperextension injury	Bilateral motor weakness: Upper limb weakness (LMN lesion) > Lower limb weakness (UMN lesion) Urinary retention	Variable bilateral suspended sensory loss Loss of pain and temperature > loss of vibration and proprioception
Posterior Cord	Posterior spinal artery infarction, trauma	Preserved	Bilateral loss of vibration, proprioception, light touch at and below the lesion Preserved pain and temperature

American Spinal Injury Association Impairment Scale

Grade	Description
A	Complete, no motor/sensory below neurological level including S4/5
B	Incomplete, sensory but not motor function preserved below neurological level including S4/5
C	Incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade <3
D	Incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade ≥3
E	Normal motor and sensory function

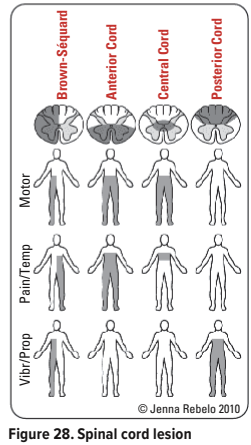


Figure 28. Spinal cord lesion syndromes

Peripheral Nerves

- see Neurology, N38

Classification

Table 23. Seddon's Classification of Peripheral Nerve Injury

Nerve Injury	Description	Recovery
Neurapraxia (class I)	Axon structurally intact but fails to function	Within h to mo (average 6-8 wk)
Axonotmesis (class II)	Axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury	Spontaneous axonal recovery at 1 mm/d, max at 1-2 yr
Neurotmesis (class III)	Nerve completely transected	Need surgical repair for possibility of recovery

Etiology

- ischemia
- nerve entrapment (compression) by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve
- direct trauma (e.g. transection)
- iatrogenic

Investigations

- clinical exam: muscle bulk and tone, power, sensation, reflexes, localization via Tinel's sign (paresthesias elicited by tapping along the course of a nerve)
- electrophysiological studies: EMG/nerve conduction study (assess nerve integrity and monitoring recovery after 2-3 wk post-injury)
- labs: blood work (e.g. CBC, TSH, vitamin B_{12}), CSF
- imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography, angiogram if vascular damage is suspected

Treatment

- early neurosurgical consultation if injury is suspected

Table 24. Treatment by Injury Type

Injury	Treatment
Entrapment	Nonsurgical: Prevent repeated stress/injury, physiotherapy, NSAIDs, local anesthesia/steroid injection Surgical: Nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management
Stretch/Contusion	Follow-up clinically for recovery; exploration if no recovery in 3 mo
Axonotmesis	If no evidence of recovery, resect damaged segment Prompt physical therapy and rehabilitation to increase muscle function, maintain joint ROM, maximize return of useful function Recovery usually incomplete
Neurotmesis	Surgical repair of nerve sheath unless known to be intact (suture nerve sheaths directly if ends approximate or nerve graft (usually sural nerve)) Clean laceration: early exploration and repair Contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 d

Complications
- loss of function (temporarily or permanently)
- neuropathic pain: with neuroma formation
- complex regional pain syndrome: with sympathetic nervous system involvement

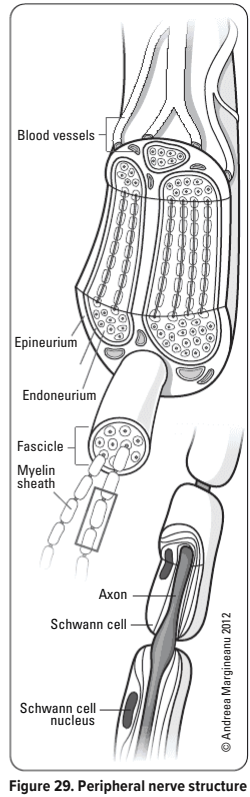


Figure 29. Peripheral nerve structure

SPECIALTY TOPICS

Neurotrauma

Trauma Management
- see Emergency Medicine, ER7

Indications for Intubation in Trauma
1. depressed or decreasing LOC (patient cannot protect airway): usually GCS ≤8
2. need for hyperventilation
3. severe maxillofacial trauma (patency of airway is doubtful)
4. need for pharmacologic paralysis for evaluation or management
   - if basal skull fracture suspected, avoid nasotracheal intubation as may inadvertently enter brain
   - note: intubation prevents patient's ability to verbalize for determining GCS

Trauma Assessment

Initial Management

ABCs of Trauma Management
- see Emergency Medicine, ER2

NEUROLOGICAL ASSESSMENT

Mini-History
- period of loss of consciousness, post-traumatic amnesia, loss of bowel/bladder control, loss of sensation, weakness, type of injury/accident
- in urgent situations, remember "SAMPLE-F": signs/symptoms, allergies, medications, PMHx, last meal, events leading up to the trauma, and baseline functioning

Neurological Exam
- ABCs
- vital signs
- GCS
- brainstem reflexes (if appropriate)
- cranial nerve exam
- motor and sensory exam, including peripheral reflexes
- spine (pain/tenderness, palpable deformity)
- sphincter tone and saddle sensation
- record and repeat neurological exam at regular intervals, as appropriate

Glasgow Coma Scale

Eye Response	Verbal Response	Motor Response
4 spontaneous	5 oriented	6 obeys commands
3 opens eyes to voice	4 confused	5 localizes to pain
2 opens eyes to pain	3 inappropriate words	4 withdraws from pain
1 no eye opening	2 incomprehensible sounds	3 flexion to pain (decorticate posturing)
	1 no response	2 extension to pain (decerebrate posturing)
	T intubated	1 no response

Best response for each component recorded individually (e.g. E3V3M5)
≥13 is mild injury; 9-12 is moderate injury; ≤8 is severe injury

Investigations
- spinal injury precautions (cervical collar) are continued until C-spine is cleared
- C, T, L-spine and head CT scan
  - AP, lateral, odontoid views for C-spine (swimmer's view if necessary)
  - C1-T1 should be well-visualized as ~50% of injuries happen at the junction of the cervical and thoracic spines
  - look for fractures, loss of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
  - rarely done: oblique views looking for pars interarticularis fracture ("Scottie dog" sign)
  - if CT is unavailable, can do C-spine x-ray with T1 well visualized, but not recommended since injuries at C and T spine junction are seldom adequately visible with x-ray
- cross and type, arterial blood gas (ABG), CBC, drug screen (especially EtOH)
- chest and pelvic x-ray as indicate

TREATMENT

Treatment for Minor Head Injury (GCS 13-15)
- observation over 24-48 h
- wake every hour
- judicious use of sedatives or pain killers during monitoring period
- outpatient: advise patients to undergo stepwise approach to return to play and return to school (for latest recommendations, refer to 2019 Parachute Canada Concussion Guidelines)

Treatment for Moderate (GCS 9-12) and Severe Head Injury (GCS ≤8)
- clear airway and ensure breathing; intubate if necessary
- secure C-spine
- maintain adequate BP
- monitor for clinical deterioration
- monitor and manage increased ICP if present (see *Herniation Syndromes, NS7*)

Admission Required if:
- skull fracture (indirect signs of basal skull fracture, see *Head Injury*)
- confusion, impaired consciousness, concussion with >5 min amnesia
- focal neurological signs, extreme H/A, vomiting, seizures
- unstable spine
- use of EtOH
- poor social support

Head Injury

Epidemiology
- M:F=2-3:1

Pathogenesis
- acceleration/deceleration: contusions, SDH, axon and vessel shearing/mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

Scalp Injury
- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

Skull Fractures
- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for ABx, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
  - internal fractures into sinus may lead to meningitis or pneumocephalus
  - risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray, rely on clinical signs
  - retroauricular ecchymosis (Battle's sign)
  - periorbital ecchymosis ("raccoon eyes")
  - hemotympanum
  - CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

- Never do LP in head injury unless increased ICP has been ruled out
- All patients with head injury have C-spine injury until proven otherwise
- Suspect hematoma in EtOH-related injuries
- Low BP after head injury means injury elsewhere
- Must clear spine both radiologically AND clinically

Comparative Effectiveness of Using Computed Tomography Alone to Exclude Cervical Spine Injuries in Obtunded or Intubated Patients: Meta-Analysis of 14327 Patients with Blunt Trauma
J Neurosurg 2011;115:541-549
Purpose: To determine the effectiveness of helical CT alone (vs. CT and adjuvant imaging such as MR) to diagnose acute unstable C-spine injury following blunt trauma.
Methods: Meta-analysis comparing modern CT with adjunctive imaging modalities.
Results: 17 studies with 14327 patients total. Sensitivity17 studies with 14327 patients total. Sensitivity and specificity for modern CT were both >99.9% (95% CI 0.99-1.00 for both). The negative predictive value of a normal CT scan was 100% (95% CI 0.96-1.00) and accuracy was not affected by the global severity of injury, CT slice thickness, or study quality.
Conclusions: CT alone is sufficient to detect unstable C-spine injuries in trauma patients and adjuvant imaging is unnecessary with a negative CT scan result. Consequently, if a CT scan is negative for acute injury, the cervical collar may be removed from obtunded or intubated trauma patients.

The Canadian CT Head Rule for Patients with Minor Head Injury
Lancet 2001;357:1391-1396
CT Head is only required for patients with minor head injuries with any one of the following:
High-Risk (for neurological intervention):
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid otorrhea/rhinorrhoea, Battle's sign)
- Vomiting ≥2 episodes
- Age ≥65 yr

Medium-Risk (for brain injury on CT):
- Amnesia after impact >30 min
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs)

Minor Head Injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

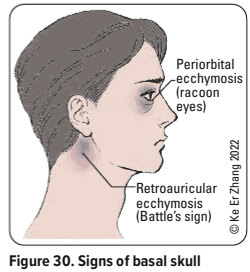


Figure 30. Signs of basal skull fractures

Cranial Nerve Injury
- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention indicated for:
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VIII: repair of ossicles
- prognoses:
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
  - CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

Arterial Injury
- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

Intracranial Bleeding
- see *Blood, NS20* and *Cerebrovascular Disease, NS22*

Brain Injury

Primary Impact Injury
- mechanism of injury determines pathology
- penetrating injuries, direct impact:
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- concussion: a trauma-induced alteration in mental status
  - refer to American Academy of Neurology (AAN) guidelines for classification and management
  - no parenchymal abnormalities on CT
- coup (damage at site of blow) and contrecoup (damage at opposite site of blow)
  - acute decompression causes cavitation followed by a wave of acute compression
- contusion (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space-occupying lesion on CT

Secondary Pathologic Processes
- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to:
  - high glutamate release → NMDA receptor activation → cytotoxic cascade
  - cerebral edema
  - intracranial hemorrhages
  - ischemia/infarction
  - raised ICP, intracranial HTN
  - hydrocephalus

Extracranial Conditions
- hypoxemia
  - due to trauma to the chest, upper airway, brainstem
  - extremely damaging to vulnerable brain cells
  - leads to ischemia, raised ICP
- hypercarbia
  - leads to raised ICP (secondary to vasodilation)
  - systemic hypotension
  - caused by blood loss (e.g. ruptured spleen)
  - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
  - leads to increased brain metabolic demands → ischemia
  - caused by severe infections (e.g. meningitis, sepsis)
- fluid and electrolyte imbalance
  - iatrogenic (most common)
  - SIADH caused by head injury
  - DI
  - may lead to cerebral edema and raised ICP
- coagulopathy

AAN Concussion Classification
Grade 1: altered mental status <15 min
Grade 2: altered mental status >15 min
Grade 3: any loss of consciousness

Concussion Grades

AAN Grade	Management Options
1	15 min for amnesia and other symptoms Return to normal activity if symptoms clear within 15 min
2	Remove from activity for 1 d, then re-examine CT or MRI if H/A or other symptoms worsen or last >1 wk Return to normal activity after 1 wk without symptoms
3	Emergent neurological exam and imaging; if initial exam is normal, may go home with close follow-up Admit if any signs of pathology or persistent abnormal mental status CT or MRI if H/A or other symptoms If brief loss of consciousness (<1 min), return to normal activity after 1 wk without symptoms If prolonged loss of consciousness (>1 min), return to normal activity only after 2 wk without symptoms

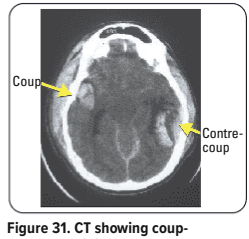


Figure 31. CT showing coup-contrecoup injury

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury
NEJM 2012;367:2471-2481
Background: ICP monitoring is frequently used to monitor severe TBI, but controversy exists over whether it is beneficial.
Methods: Study sample (n=324 patients, ≥13 yr) consisted of those who had severe TBI and were being treated in ICU in Bolivia or Ecuador. Patients were randomly assigned to one management group:
1. ICP-monitoring based management.
2. Management based on imaging and clinical examination.

Primary outcome was a composite of survival time, impaired consciousness, functional status (at 3, 6 mo), and neuropsychological status (at 6 mo).
Results: No significant difference between management groups based on primary outcome, 6 mo mortality, median length of ICU stay, or occurrence of serious adverse events. However, duration of brain-specific treatments (e.g. use of hyperosmolar fluids or hyperventilation) was higher in the imaging-clinical examination group (4.8 d vs. 3.4 d, P=0.002).
Conclusion: Maintaining monitored ICP at 20 mmHg or less is not superior to care based on imaging and clinical examination.

Intracranial Conditions
- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

Brain Injury Outcomes
- mildly traumatic (GCS 13-15): post-concussive symptoms: H/A, fatigue, dizziness, nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
- moderately traumatic (GCS 9-12): outcome proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

Late Complications of Head/Brain Injury
- seizures: 5% of head injury patients develop seizures
  - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
  - post-traumatic seizure may be immediate, early, or late
  - presence of early (within first week) post-traumatic seizure raises incidence of late seizures
- meningitis: associated with CSF leak from nose or ear
- hydrocephalus: acute hydrocephalus or delayed NPH
- Post-Concussion Syndrome: H/A, dizziness, cognitive changes, psychological symptoms, and behavioural symptoms

Spinal Cord Injury

- see Orthopedic Surgery, OR25 and Emergency Medicine, ER9

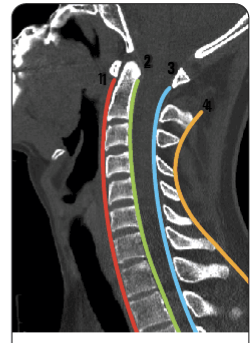
Neurogenic and Spinal Shock
- neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by:
  - interruption of sympathetics (unopposed parasympathetics) below the level of injury, usually with injuries above T6 level
  - loss of muscle tone due to skeletal muscle paralysis below level of injury → venous pooling (relative hypovolemia)
  - neurogenic shock is to be distinguished from hemodynamic shock due to blood loss from associated wounds (true hypovolemia)
    - neurogenic shock → hypotension, bradycardia, warm and well-perfused extremities
    - hemodynamic shock → suspect in multisystem trauma and if there is peripheral vascular shut-down
- spinal shock: transient loss of all neurologic function below the level of the SCI, associated with loss of bulbocavernosus reflex, flaccid paralysis and areflexia for variable periods

Whiplash-Associated Disorders
- **definition**: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck

Initial Management of Spinal Cord Injury
- major causes of death in SCI are aspiration and shock
- the following patients should be treated as having a SCI until proven otherwise:
  - all victims of significant trauma
  - minor trauma patients with decreased LOC or complaints of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

Stabilization and Initial Evaluation in the Hospital
1. ABCs, immobilization (backboard/head strap), oxygenation, Foley catheter to urometer, temperature regulation
2. hypotension: maintain sBP >90 mmHg with pressors (dopamine), hydration, and atropine
   - deep vein thrombosis (DVT) prophylaxis
3. monitor CBC/electrolytes
4. perform a mental status and CN function assessment as many patients with SCI have co-occurring traumatic brain injury
5. focused history and exam as the patient is being immobilized (see *Trauma Assessment, NS35*)
6. spine palpation: point tenderness or deformity
7. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
8. sensory level assessment: pinprick, light touch, and proprioception
9. evaluation of reflexes
10. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
11. radiographic evaluation
    - 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction (note plain films have been largely supplanted by CT)
    - flexion-extension views to disclose occult instability
    - CT scan (bony injuries); typically most trauma centres use CT as the modality of choice for looking at fractures; very sensitive with the high-resolution scanners
    - MRI mandatory if neurological deficits (soft tissue injuries); MRI can also be helpful to assess for ligamentous injury and disc herniation

SIADH → hyponatremia
DI → hypernatremia



ABCDS

Alignment
columns
anterior vertebral line (1)
posterior vertebral line (2)
spinolaminar line (3)
posterior spinous line (4)

Bone
vertebral bodies
facets
spinous processes

Cartilage

Disc
disc space
interspinous space

Soft tissues

Pre-vertebral soft tissues (A)

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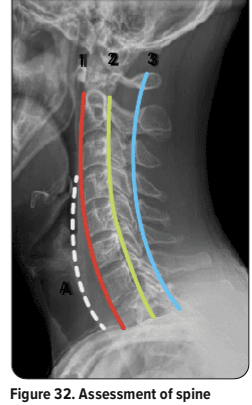

Figure 32. Assessment of spine CT/X-Ray (parasagittal view)
Images used with permission from Dr. Ferco Berger and Dr. Michael O'Keeffe

- if one fracture has been detected - the entire spine should be scanned (CT) to assess for a second lesion (can occur in 15% of spine fractures)

Medical Management Specific to Spinal Cord Injury

- option: methylprednisolone (given within 8 h of injury) is controversial; must confer with Neurosurgery service
- surgical decompression and stabilization is recommended within 24 h of all types of severe SCI (AIS A-C) regardless of level, provided the patient is medically stable
- the management of milder forms of SCI, especially central cord, is more controversial although surgery is the generally preferred option

Resolution of spinal shock is indicated by the return of reflexes (most commonly the bulbocavernosus reflex)

See Landmark Neurosurgery Trials table for more information on the STASCIS trial for effectiveness of early vs. late decompressive surgery for traumatic cervical spinal cord injury.

Fractures of the Spine

FRACTURES OF THE CERVICAL SPINE

Types of Injury

Table 25. AO Spine Upper Cervical Spine Injury Classification System

Type	Description
1	Occipital condyle and occipital cervical joint complex injuries
2	C1 ring and C1-2 joint complex injuries
3	C2 and C2-3 joint complex injuries

*A, B, and C sub-categorizations apply to each type of injury
A → bony injuries only (stable)
B → tension band injuries (potentially unstable)
C → translational injuries (unstable)

Table 26. Fracture Patterns of the Cervical Spine

Fracture Type	Description
C1 Vertebral Fracture (Jefferson fracture)	Vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing its lateral masses outward and disrupting its ring Also can cause an occipital condylar fracture
Odontoid Fracture	Causes C1 and odontoid of C2 to move independently of C2 body This occurs because Normally C1 vertebra and odontoid of C2 are a single functional unit Alar and transverse ligaments on posterior aspect of odontoid usually remain intact after injury Patients often report a feeling of instability and present holding their head with their hands Type II fracture the most common
C2 Vertebral Fracture (hangman fracture)	Bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3 (spondylolisthesis of axis) Usually neurologically intact
Clay-Shoveler Fracture	Avulsion of spinous process, usually C6 or C7

The AO Spine classification is preferred to characterize fractures of the cervical spine, but the terminology described above may still be encountered on the wards

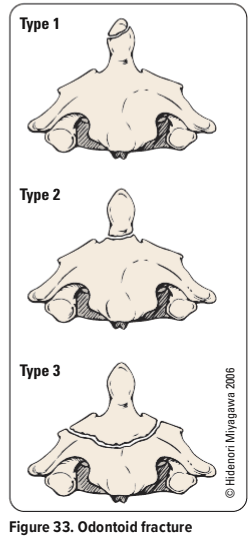

Figure 33. Odontoid fracture classification

Imaging

- AP spine x-ray (open-mouth and lateral view), CT

Treatment

- immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
- type II and III odontoid fractures: consider surgical fixation for comminution, displacement, or inability to maintain alignment with external immobilization
  - type II odontoid fractures more likely to require surgery than type III due to higher risk of non-union (fracture line in watershed zone)
- confirm stability after recovery with flexion-extension x-rays

FRACTURES AND FRACTURE-DISLOCATIONS OF THE THORACIC AND LUMBAR SPINE

- assess ligamentous injury/instability using MRI ± flexion/extension x-ray views
- thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
  - anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
  - middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
  - posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous, and ligamentum ligaments

Table 27. AO Spine Classification System for Subaxial Cervical Spine Injury and Thoracolumbar Spine Injury

Type	Description
A	**Compression fractures** Involves anterior elements (vertebral body and/or disc)
0	No injury/process fracture
1	Wedge compression (fracture of single endplate w/o involvement of posterior vertebral body wall)
2	Split/pincer type (fracture of both endplates w/o involvement of posterior vertebral body wall)
3	Incomplete burst (involvement of posterior vertebral body wall and only a single endplate)
4	Complete burst (involvement of posterior vertebral body wall and both endplates)
B	**Tension band injuries**
1	Posterior transoesseous disruption
2	Posterior ligamentous disruption
3	Anterior ligamentous disruption
C	**Translation injuries (displacement/dislocation)**
F (only for subaxial cervical spine injury)	**Facet injuries**
1	Non-displaced facet fracture (fragment <1 cm, <40% lateral mass)
2	Facet fracture with potential for instability (fragment >1 cm, >40% lateral mass or displaced)
3	Floating lateral mass (disconnection of superior and inferior articular processes)
4	Pathologic subluxation or dislocated facet

Management of Thoracolumbar Injury
- severity and management based on thoracolumbar injury classification and severity (TLICS) classification

Thoracolumbar Injury Classification and Severity Scoring

Parameter	Points
Morphology	
Compression fracture	1
Burst fracture	2
Translational/rotational fracture	3
Distraction	4
Neurologic Status	
Intact	0
Nerve root injury	2
Spinal Cord Status	
Incomplete	3
Complete	2
Cauda equina	3
Posterior Ligamentous Complex	
Intact	0
Injury suspected/indeterminate	2
Injured	3

TLICS scoring based on morphology of injury, status of posterior ligamentous complex, and neurological status
Non-operative management if TLICS = 0-3, operative management if TLICS = 5+, either operative or non-operative if TLICS = 4

Neurologically Determined Death

Definition
- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascular activity may persist for up to 2 wk

Criteria of Diagnosis
- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature >32°C, no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes: pupillary light reflex, corneal reflexes, oculocephalic response, caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water; allow 1 min after injection, 5 min between sides), pharyngeal and tracheal reflexes, cough with tracheal suctioning, absent respiratory drive at $PaCO_2$ ≥60 mmHg, ≥20 mmHg rise above baseline, and pH ≤7.28 (apnea test)
- 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
- confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

Coma

Definition
- an unrousable state in which patients show no meaningful response to environmental stimuli

Pathophysiology
- lesions affecting the cerebral cortex bilaterally, the reticular activating system, or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

Classification
- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the reticular activating system (RAS) or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B12)
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
  - infections (meningitis, encephalitis)
  - trauma (concussion, diffuse shear axonal damage)

Prenatal vs. Postnatal Repair of Myelomeningocele (MMC)
NEJM 2011;364:993-1004
Purpose: To compare outcomes of in utero repair of MMC with standard postnatal repair of MMC.
Methods: RCT comparing prenatal surgery (before 26 wk of gestation) and standard postoperative surgery. 12 mo outcomes included **death or need for placement of a CSF shunt. 30 mo outcomes included mental development and motor function.**
Results: 40% of prenatal surgery patients, compared to 82% of postnatal surgery patients, required CSF shunt (P<0.001). Prenatal surgery resulted in improvement in mental development and motor function (P=0.007). However, prenatal surgery was associated with an increased **risk of gynaecological complications.**
Conclusion: Prenatal surgery for MMC reduced the need for shunting and improved motor outcomes but was associated with maternal and fetal risks related to preterm delivery.

Investigations and Management
- ABCs
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP (after ruling out space-occupying lesion/increased ICP), EEG

Persistent Vegetative State

Definition
- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- "awake but not aware"
- follows comatose state

Etiology/Prognosis
- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

Pediatric Neurosurgery

Spinal Dysraphism

- spinal dysraphism refers to a spectrum of congenital anomalies resulting in a defective neural arch through which CNS elements are herniated
- the spectrum is divided largely into aperta (visible lesion; no skin covering) and occulta (no visible lesion; skin covering)

Table 28. Summary of Spinal Dysraphic Anomalies

	Spina Bifida Occulta	Meningocele (Spinal Bifida Aperta)	Myelomeningocele (Spina Bifida Aperta)
Definition	Congenital absence of a spinous process and a variable amount of lamina No visible exposure of meninges or neural tissue	Herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue	Herniation of meningeal and CNS tissue through a defect in the spine
Epidemiology	15-20% of the general population; most common at L5 or S1		0.1-0.2% of live births
Etiology	Failure of fusion of vertebral bodies resulting from abnormal fusion of posterior vertebral arches	Failure of fusion of posterior neural arch	Primary failure of neural tube closure
Clinical Features	No obvious clinical signs Presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia)	Most common in lumbosacral area Usually no disability, low incidence of associated anomalies, and hydrocephalus	Sensory and motor changes distal to anatomic level producing varying degrees of weakness Urinary and fecal incontinence Hydrocephalus (65-85% of patients) Most have Type II Chiari malformation (see *Chiari Malformations, NS43*)
Investigations	Plain film: Absence of the spinous process and minor amounts of the neural arch U/S, MRI to exclude spinal anomalies	Plain films, CT, MRI, U/S, echo, GU investigations	Plain films, CT, MRI, U/S, echo, GU investigations
Treatment	Requires no treatment	Surgical excision and tissue repair	Surgical closure to preserve neurologic status and prevent CNS infections Closure *in utero* shown to decrease hydrocephalus and improve postnatal motor scores
Prognosis	Generally good prognosis	Good prognosis with surgical treatment	Operative mortality close to 0%, 95% 2-yr survival 80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence Early mortality: usually due to Chiari malformation complications (respiratory arrest, aspiration), late mortality: due to shunt malfunction

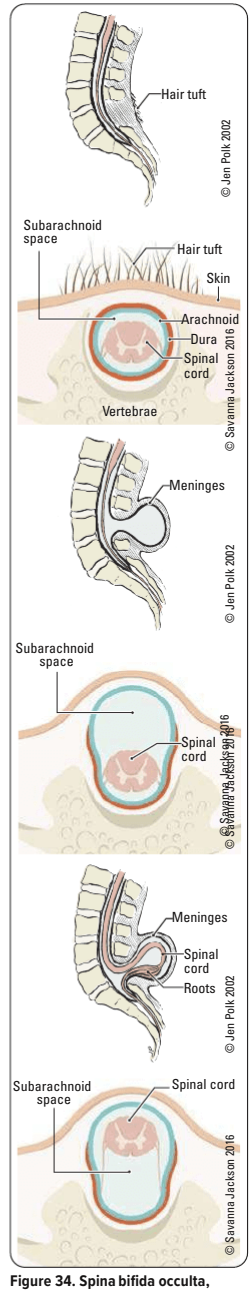

Figure 34. Spina bifida occulta, meningocele, myelomeningocele

Intraventricular Hemorrhage

Definition
- hemorrhage originating in the periventricular subependymal germinal matrix

Epidemiology
- incidence and severity increases as gestational age (GA) and birth weight (BW) decrease
- 50% of IVH occurs within 8 h of birth; 90% occurs by day 3

Risk Factors
- prematurity (<32 wk GA), BW <1500 g, need for vigorous resuscitation at birth, pneumothorax, ventilated preterm infants, hemodynamic instability, respiratory distress syndrome (RDS), chorioamnionitis, coagulopathy

Clinical Features
- many infants with IVH are asymptomatic
- subtle signs: altered LOC, decreased tone and/or activity, hypoventilation/apnea
- catastrophic deterioration: may have bulging fontanelle, apnea/hypoventilation, hypotension, bradycardia, cranial nerve abnormalities, sudden drop in hematocrit, metabolic acidosis, seizures, coma

Diagnosis
- head U/S is preferred imaging modality
- routine head U/S screening conducted for all preterm infants <32 wk GA or <1500 g gestation throughout NICU stay
- IVH graded using Papile classification
- parenchymal hemorrhage may also occur in the absence of IVH

Management of Acute Hemorrhage
- supportive care to maintain blood volume, cerebral perfusion, and acid-base status
- follow up with serial imaging

Prognosis
- outcome largely dependent on grade of IVH, with grades I and II having a relatively favourable prognosis
- greatest morbidity and mortality is seen with grade IV IVH and development of posthemorrhagic hydrocephalus requiring VP shunt placement
- short-term sequelae for severe IVH: mortality, extension of bleed, posthemorrhagic hydrocephalus, posthemorrhagic infarction, cyst formation
- possible long-term major neurological sequelae: cerebral palsy (CP), cognitive deficits, motor deficits, visual and hearing impairment

Papile Classification
Grade I: germinal matrix hemorrhage

Grade II: IVH without ventricular dilation

Grade III: IVH with ventricular dilation

Grade IV: IVH with parenchymal extension

Hydrocephalus in Pediatrics

Etiology
- congenital
  - aqueductal anomalies, primary aqueductal stenosis in infancy
  - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  - Dandy-Walker malformation (2-4%)
  - Chiari malformation, especially type II (see *Table 29, NS43*)
  - MMC
- acquired
  - post meningitis
  - post hemorrhage (SAH, IVH)
  - masses (vascular malformation, neoplastic)

Clinical Features
- symptoms and signs of hydrocephalus are age related in paediatrics
- increased head circumference, bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding, and vomiting
- "cracked pot" sound on cranial percussion
- scalp vein dilation (increased collateral venous drainage)
- "sunset eyes"
- episodic bradycardia and apnea

Investigations
- skull x-ray, U/S, CT, MRI, ICP monitoring

Treatment
- similar to adults (see *Hydrocephalus, Treatment, NS10*)

Dandy-Walker Malformation

Definition
- atresia of foramina of Magendie (median aperture) and Luschka (lateral apertures), resulting in:
  - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic cerebellar hemispheres
  - posterior fossa cyst, enlarged posterior fossa
  - dilation of 4th ventricle (also 3rd and lateral ventricles)
  - can be detected in utero
- associated anomalies
  - hydrocephalus (90%)
  - agenesis of corpus callosum (17%)
  - occipital encephalocele (7%)

Epidemiology
- 2-4% of pediatric hydrocephalus

Clinical Features
- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

Investigations
- ultrasound, CT, MRI

Treatment
- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
  - e.g. VP shunt, cystoperitoneal shunt, lumboperitoneal shunt, VA shunt, lumbar drain

Prognosis
- 75-100% survival, 50% have normal IQ

Chiari Malformations

Definition
- malformations at the medullary-spinal junction

Etiology
- unclear, likely maldevelopment/dysgenesis during fetal life

Categories

Table 29. Categories of Chiari Malformations

	Type I	Type II
Definition	Cerebellar tonsils lie below the level of the foramen magnum	Part of cerebellar vermis, medulla, and 4th ventricle extend through the foramen magnum often to midcervical region
Epidemiology	Average age at presentation 15 yr	Present in infancy
Clinical Features	Many are asymptomatic Pain (69%), weakness (56%), numbness (52%), loss of temperature sensation (40%) Central cord syndrome (65%) Foramen magnum compression syndrome (22%), cerebellar syndrome (11%), syringomyelia (50%), hydrocephalus (10%)	Findings due to brainstem and lower cranial nerve dysfunction Neurogenic dysphagia (69%), apnea (58%), stridor (56%), aspiration (40%), arm weakness (27%), downbeat nystagmus Respiratory arrest is the most common cause of mortality Usually associated with MMC and hydrocephalus
Investigations	MRI	MRI
Treatment	Symptomatic patients (early surgery recommended; <2 yr post symptom onset) → suboccipital craniectomy, duraplasty	Preserved When symptomatic, check the shunt first. Then consider surgical decompression (which does not reverse intrinsic brainstem abnormalities) → cervical laminectomy, duraplasty

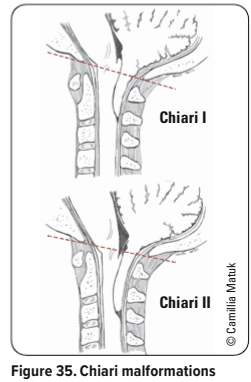

Figure 35. Chiari malformations

Craniosynostosis

Definition
- premature closure of the cranial suture(s)

Classification
- sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
- coronal: expansion in superior and lateral direction (brachycephaly)
- metopic (trigonocephaly)
- lambdoid: least common

Epidemiology
- 0.6 in 1000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

Clinical Features
- skull deformity, raised ICP ± hydrocephalus
- ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
- must differentiate from positional plagiocephaly (secondary to persistently/exclusively sleeping on back)

Investigations
- plain radiographs, CT scan

Treatment
- parental counselling about nature of deformity, associated neurological symptoms
- surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

Pediatric Brain Tumours

- see *CNS Tumours, NS12*

Most Common Pediatric Brain Tumours
Astrocytoma, low-grade
Supratentorial
Infratentorial
Medulloblastoma
Ependymoma
Glioblastoma

Epidemiology
- 20% of all paediatric cancers (second only to leukemia)
- 60% of paediatric brain tumours are infratentorial
- paediatric brain tumours arise from various cellular lineages:
  - neural (stem) cells: low-grade astrocytoma (supra- or infratentorial), high-grade astrocytoma, glioblastoma (largely supratentorial) (see *Adult Diffuse Gliomas, NS15*)
  - primitive nerve cells: supratentorial PNET
  - non-neuronal (stem) cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma (schwannoma), pituitary adenoma, etc.
- 90% of neonatal brain tumours are infratentorial (medulloblastoma) or pineal gland (pineoblastoma)

Clinical Features
- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escapes diagnosis due to expansile cranium and neural plasticity in children

Table 30. Overview of Childhood Primary Brain Tumours*

Type	Overview
Pilocytic (low-grade) Astrocytoma	Usually in posterior fossa
	Well circumscribed
	Benign, good prognosis
Medulloblastoma	PNET
	In cerebellum → compresses 4th ventricle → hydrocephalus
	Highly malignant
Ependymoma	In 4th ventricle → hydrocephalus
	Poor prognosis
Hemangioblastoma	Often cerebellar
	Associated with von Hippel-Lindau syndrome with retinal angiomas
	Can produce erythropoietin (EPO) → secondary polycythemia
Craniopharyngioma	Causes bitemporal hemianopia (thus often confused with pituitary adenoma)
	Most common supratentorial childhood tumour
	Benign

* See also, Medical Genetics, Table 5. *Examples of Familial Cancer Syndromes*, MG7

Functional Neurosurgery

Movement Disorders

- see Neurology, *Parkinson's Disease*, N33, *Dystonia*, N34, and *Multiple Sclerosis*, N55

Table 31. Surgical Targets for Movement Disorders

Disorder	Indications	Procedures	Outcomes	Morbidity
Parkinson's Disease	Intractable contralateral bradykinesia/tremor Failure of medical management (advanced disease) Drug-induced dyskinesias (see dystonia, below)	Simultaneous, bilateral surgery/stimulation is most common Preferred target: anterodorsal subthalamic nucleus Other targets: stereotactic ablation (pallidotomy) or stimulation of posteroventral GPi Stimulation of caudal zona incerta Parkinsonian tremor: stereotactic ablation (thalamotomy) or stimulation of ventral intermediate (Vim) nucleus of thalamus	39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores Reduced dosage of medications (STN) More effective than medical management in advanced Parkinson's Disease (PD) Early intervention may reduce severity, course, and progression of disease Less effective for patients with atypical presentations	IH, infection, seizure (1%-4%) Paresthesias Involuntary movements Cognitive functioning: decreased lexical fluency, impaired executive function (STN>GPi) Psychiatric: depression, mania, anxiety, apathy (STN>GPi)
Dystonia	Contralateral primary (generalized) dystonias; cervical and tardive dystonias Contralateral secondary dyskinesia (i.e. drug-induced: L-dopa, neuroleptics)	Preferred target (primary dystonia): Stereotactic ablation (pallidotomy) or stimulation of posteroventral GPi Secondary dystonia: stimulation of anterodorsal STN Stimulation of VPL thalamic nucleusStimulation of VPL thalamic nucleus	Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDS) score Secondary dystonia: 62-89% improvement in dystonias Delayed effects: wk to mo	ICH, infection, seizure (1%-4%) Minor effects on cognitive functioning (especially decreased lexical fluency; STN>GPi)
Tremor	Contralateral appendicular essential tremor (ET) (first disorder to be treated by DBS; DBS is viable alternative to Rx) Intention tremor resulting from demyelination of cerebellar outflow tracts (e.g. in multiple sclerosis) Brainstem tremor (Holmes tremor)	Preferred target: stereotactic aPreferred target: stereotactic ablation (thalamotomy) or stimulation of Vim nucleus of thalamus Other targets: stimulation of caudal zona incerta Parkinsonian tremor: stimulation of anterodorsal STN	Durable reductions in essential tremor rating scale (ETRS) scores Reduced dosage of medications Conflicting data on vocal/facial tremor	ICH, infection, seizure (1%-4%) Paresthesias/pain Dysarthria Ataxia Minor effects on cognitive functioning (especially decreased lexical fluency) Tolerance may develop over time

Neuropsychiatric Disorders

- see Neurology, N21 and Psychiatry, *Obsessive Compulsive Disorder*, PS19 and *Depressive Disorders*, PS12
- psychiatric neurosurgery indicated only for severe symptoms that are refractory to medical management

Table 32. Surgical Targets for Neuropsychiatric Disorders

Disorder	Procedures	Outcomes	Morbidity
Obsessive Compulsive Disorder (OCD)	Anterior capsulotomy/stimulation of the anterior limb of the IC	Currently under investigation Reportedly 25-75% response rate	ICH (1-2%) Mild effects on cognitive functioning Anxiety ± panic disorder (case report)
Tourette's Syndrome	Stimulation of midline intralaminar nuclei of the thalamus Stimulation of motor and limbic portions of GPi Stimulation of the anterior limb of the IC	Currently under investigation Reportedly >70% reduction in vocal or motor tics and urge	ICH (1-2%) Mild sexual dysfunction
Major Depressive Disorder (MDD)	Stimulation of the subgenual cingulate cortex Anterior capsulotomy or stimulation of the anterior limb of the IC	Currently under investigation Reportedly 60% response rate; 35% remission rate	ICH (1-2%) Pain, H/A Worsening mood, irritability

- other experimental indications include: anorexia nervosa, substance use disorders, and functional neurological disorders, amongst others

Consensus on Guidelines for Stereotactic Neurosurgery for Psychiatric Disorders
Journal of Neurology, Neurosurgery & Psychiatry 2014;85(9):1003-1008
- Stereotactic ablative procedures such as cingulotomy and capsulotomy for MDD and OCD lack level I evidence.
- DBS in any brain target attempted so far is considered "investigational."
- Multidisciplinary teams are mandatory to ensure safe and ethical conduct in psychiatric neurosurgery, with particular attention directed to ensuring treatment refractoriness, consent procedures, patient capacity and autonomy, and extensive pre-/postoperative assessments.

Chronic Pain

Table 33. Surgical Targets for Chronic Pain

Disorder	Indications	Procedures	Outcomes	Morbidity
Neuropathic Pain	Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, postoperative neuropathic pain, complex regional pain syndrome)	Preferred target: stimulation of the contralateral VPL VPM thalamic nuclei ± PVG/PAG Other targets: stimulation of the contralateral IC Stimulation of the contralateral motor cortex For postoperative neuropathic pain, surgical procedure may be aimed at correcting any identifiable residual deformity from prior spine surgery Surgery is not primary modality if no structurally correctable radiologic findings	47% improvement in perception of pain intensity Less favourable results in central pain syndromes and poorly localized pain	ICH (1-2%) Paresthesia Anxiety ± panic disorder
Nociceptive Pain	Severe, intractable, organic nociceptive pain	Bilateral (most common) stimulation of the PVG/PAG	Reportedly 63% improvement in perception of pain intensity	ICH (1-2%) Paresthesia Anxiety ± panic disorder

Surgical Management of Epilepsy

- see Neurology, N20 for the medical treatment of epilepsy

Indications

- medically refractory seizures, usually defined as recurrent seizures resistant to two first-line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG/SEEG, MRI, and neuropsychological testing; other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

Procedure

- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common
- vagus nerve stimulation
- DBS

Outcomes

- 41-79% of adult patients are seizure-free for 5 yr after temporal lobe resection
- 58-78% of children are seizure-free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions, such as depression and anxiety, as well as improvement in quality of life measures

Morbidity

- 0.4-4% of surgical patients will have partial hemianopia, aphasia, motor deficit, sensory deficit, or CN palsy following anteromedial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 yr

Predictors

- positive predictive factors for seizure freedom following anteromedial temporal lobectomy include:
  - hippocampal sclerosis (unilateral)
  - focal localization of interictal epileptiform discharges
  - absence of preoperative generalized seizures
  - tumoural etiology
  - complete resection of the lesion
- ongoing research on neuroimaging biomarkers to predict treatment response, especially to neuromodulation

Timing of Referral to Evaluate for Epilepsy Surgery: Expert Consensus Recommendations from the Surgical Therapies Commission of the International League Against Epilepsy.
Epilepsia. 2022;63(10):2491-2506.
Purpose: To develop a set of recommendations to guide clinicians caring for patients with epilepsy on when to refer patients for surgical evaluation.
Methods: Delphi consensus process took place with 61 clinicians with a median of 22 years in practice from 28 countries to reach agreement on indications for surgical referral for epilepsy treatment.
Results: (1) Referral should be made for every patient with drug-resistant epilepsy, as soon as drug resistance is ascertained; (2) Referral should be considered for older patients with drug-resistant epilepsy who have no surgical contraindications; (3) Referral should be considered in patients who are seizure-free on 1-2 medications, but have a brain lesion in non-eloquent cortex; and (4) Referral should not be offered to patients with active substance use problems, who are uncooperative with management.
Conclusions: Expert consensus on providing referrals for consideration of surgical management of epilepsy are presented.

Surgical Management for Trigeminal Neuralgia

• reserved for cases refractory to medical management; see Neurology, N44 for medical management

Surgical Options

• trigeminal nerve branch procedures
  - local blocks (phenol, alcohol)
  - neurectomy of the trigeminal branch
  - nerve branches
    - V_1 block at the supraorbital, supratrochlear nerves
    - V_2 block at the foramen rotundum or infraorbital nerves
    - V_3 block at the foramen ovale
• percutaneous trigeminal rhizotomy
  - glycerol injection
  - mechanotrauma via catheter balloon
• radiofrequency thermocoagulation
• Gamma Knife radiosurgery
• microvascular decompression
  - posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable Teflon® felt

Landmark Neurosurgery Trials

Trial Name	Reference	Clinical Trial Details
CNS TUMOURS		
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma	NEJM 2005;352:987–996	**Title**: Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma **Purpose**: To compare the safety and efficacy of adjuvant XRT alone with adjuvant XRT plus temozolomide, given with and after XRT. **Methods**: Patients with newly diagnosed glioblastoma were randomly assigned to receive XRT alone or XRT plus continuous daily temozolomide, followed by 6 cycles of adjuvant temozolomide. The primary endpoint was overall survival. **Results**: The two-year survival rate was 26.5% with XRT plus temozolomide compared to 10.4% with XRT alone. The addition of temozolomide resulted in grade 3 or 4 hematologic toxic effects in 7% of patients. **Conclusions**: The addition of temozolomide to XRT provides a significant survival benefit for newly diagnosed glioblastoma.
Postoperative Radiotherapy in the Treatment of Single Metastases to the Brain: A Randomized Trial	JAMA 1998;280(17):1485-1489	**Title**: Postoperative Radiotherapy in the Treatment of Single Metastases to the Brain: A Randomized Trial **Purpose:** To assess the natural history of unruptured intracranial aneurysms and to measure the risk associated with the repair. **Methods:** 4060 patients were enrolled and non-randomly assigned to operative (surgical or endovascular repair) or nonoperative groups based on the planned management. Patients were eligible if they had at least one UIA with or without aneurysmal symptoms. **Results:** Without surgery, 5 yr rupture rates for aneurysms were progressively higher for larger sized aneurysms. These rates are slightly higher for aneurysm in the posterior circulation. These rates were similar or worse with surgical or endovascular repair of similar lesions, with age of the patient and size and location of the aneurysm being predictors of outcome. **Conclusions:** In clinical decision-making, site, size, and group specific risks of the natural history should be weighed against the site, size, and age-specific risks of repair for each patient.
CEREBROVASCULAR DISEASE		
ISUIA	Lancet 2003;362:103-110	**Title**: Unruptured Intracranial Aneurysms: Natural History, Clinical Outcome, and Risks of Surgical and Endovascular Treatment **Purpose**: To assess the natural history of unruptured intracranial aneurysms and to measure the risk associated with the repair. **Methods**: 4060 patients were enrolled and non-randomly assigned to operative (surgical or endovascular repair) or nonoperative groups based on the planned management. Patients were eligible if they had at least one UIA with or without aneurysmal symptoms. **Results**: Without surgery, 5 yr rupture rates for aneurysms were progressively higher for larger sized aneurysms. These rates are slightly higher for aneurysm in the posterior circulation. These rates were similar or worse with surgical or endovascular repair of similar lesions, with age of the patient and size and location of the aneurysm being predictors of outcome. **Conclusions**: In clinical decision-making, site, size, and group specific risks of the natural history should be weighed against the site, size, and age-specific risks of repair for each patient.
STICH	Lancet 2005;365(9457):387-97	**Title**: Early Surgery versus Initial Conservative Treatment in Patients with Spontaneous Supratentorial Intracerebral Haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a Randomised Trial **Purpose**: To compare early surgery and initial conservative treatment for intracerebral haemorrhage. **Methods**: Patients were randomized to either the early surgery group (combined haematoma evacuation with medical treatment within 24 h) or the initial conservative treatment group (medical treatment, later evacuation if necessary). Patients were divided based on prognosis at 6 mo, with a good prognosis group (favourable outcome) being defined as good recovery or moderate disability on the Glasgow outcome scale. **Results**: 26% of patients with intracerebral hemorrhage treated with early surgery had favourable outcomes compared to 24% of patients with intracerebral hemorrhage treated with initial conservative treatment, but this difference was not statistically significant (P=0.414) **Conclusions**: There is no additional benefit of early surgery compared to initial conservative treatment in the treatment of patients with spontaneous intracerebral hemorrhage.
DESTINY	Stroke 2007;38(9): 2518-2525	**Title**: Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial **Purpose**: To assess the role of decompressive surgery in reducing mortality following massive cerebral infarction. **Methods**: 32 patients were randomized to either the hemicraniectomy or conservative management group. **Results**: 88% and 47% of patients in the decompressive surgery and conservative management group survived 30 d following cerebral infarction (P=0.02). **Conclusions**: In patients with malignant infarction of the MCA, hemicraniectomy reduces mortality.

Trial Name	Reference	Clinical Trial Details
DECIMAL	Stroke 2007;38:2506-2507	**Title**: Sequential Design, Multicenter, Randomized Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarction (DECIMAL Trial) **Purpose**: To assess the efficacy of early decompressive craniectomy in patients with malignant MCA infarction. **Methods**: 38 patients were randomized to receive early decompressive craniectomy plus standard medical therapy or standard medical therapy alone. **Results**: Moderate disability at 6 mo and 1 yr were 25% and 50% for the surgery group and 5.6% and 22% for the no-surgery group. There was a 52.8% absolute reduction of death following surgery compared to medical management. **Conclusions**: Early decompressive craniectomy in patients with malignant MCA infarction reduces mortality rate, but with greater rates of moderate disability.
HAMLET	Lancet Neurol 2009;8(4):326-333	**Title**: Surgical Decompression for Space-occupying Cerebral Infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): A Multicentre, Open Randomised Trial **Purpose**: To assess the effect of decompressive surgery within 4 d of onset of symptoms in patients with space-occupying hemispheric infarction. **Methods**: 64 patients were assigned within 4 d of stroke onset to either surgical decompression or best medical treatment. **Results**: Surgical decompression had no effect on functional outcome at 1 yr, but resulted in a case fatality absolute risk reduction of 38%. A meta-analysis of DESTINY, DECIMAL, and HAMLET studies showed that patients who were randomized to surgical decompression within 48 h of stroke onset had reduced poor outcomes and case fatality. **Conclusions**: Surgical decompression reduces case fatality and poor outcome in patients with space-occupying infarctions when initiated within 48 h of stroke onset. No evidence of improved functional outcome if delayed up to 96 h after stroke onset.
CLEAR III	Lancet 2017; 389(10069): 603-611	**Title**: Thrombolytic Removal of Intraventricular Haemorrhage in Treatment of Severe Stroke: Results of the Randomised, Multicentre, Multiregion, Placebo-controlled CLEAR III Trial **Purpose**: Purpose: To study the effect of alteplase versus saline irrigation on improving functional outcomes in patients with intraventricular hemorrhage. **Methods**: The study involved 500 patients who had an EVD, stable, non-traumatic ICH volume under 30 mL, IVH obstructing the 3rd or 4th ventricles, and no underlying pathology. The participants were randomized to receive either alteplase 1 mg, 12 doses 8 h apart or 0.9% saline through the EVD. **Results**: A good functional outcome (modified Rankin score) of 3 or less at 180 d was reached in 48% and 45% in the alteplase and saline group respectively (risk ratio 1·06 (95% CI 0·88–1·28; P=0·554)). **Conclusions**: Patients with IVH who have an EVD do not have significantly improved functional outcomes with alteplase irrigation as compared with saline irrigation.
NEUROTRAUMA		
MRC CRASH	Lancet 2004;365:1321-1328	**Title**: Final Results of MRC CRASH, a Randomised Placebo-controlled Trial of Intravenous Corticosteroid in Adults with Head Injury - Outcomes at 6 Months **Purpose**: To examine the effect of corticosteroids on death and disability after head injury. **Methods**: 10008 patients with head injury and a GCS≤14 within 8 h of injury were randomized to receive a 48-h infusion of corticosteroid (methylprednisolone) or placebo. **Results**: The risk of death was higher in the corticosteroid group compared to the placebo group (P=0.0001), as was the risk of death or severe disability (P=0.079). There was no evidence that the effect of corticosteroids differed by injury severity or time since injury. **Conclusions**: Corticosteroids should not be used to treat head injury of any severity.
DECRA	NEJM 2011;364:1493-1502	**Title**: Decompressive Craniectomy in Diffuse Traumatic Brain Injury **Purpose**: To determine if decompressive craniectomy improves functional outcomes in patients with severe TBI and refractory elevated intracranial pressure. **Methods**: 155 patients with severe diffuse TBI and refractory intracranial hypertension were randomized to receive either bifrontotemporoparietal decompressive craniectomy or standard care. The final primary outcome was the Extended Glasgow Outcome Scale 6 mo post-injury. **Results**: Compared to patients who received standard care, those in the craniectomy group had less time with intracranial pressures above the treatment threshold (P<0.001) and fewer days in the intensive care unit (P<0.001). However, those with a craniectomy had poorer scores on the Extended Glasgow Outcome Scale (P=0.03) and a greater risk of unfavourable outcome (P=0.02). **Conclusions**: In patients with severe diffuse TBI and persistent intracranial hypertension, early bifrontotemporoparietal decompressive craniectomy decreases intracranial pressure and ICU stay but is associated with poorer outcomes.
BEST:TRIP	NEJM 2012;367:2471–2481	**Title**: A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury **Purpose**: To determine whether the information derived from the monitoring of ICP in patients with severe TBI improves medical practice and patient outcomes. **Methods**: 324 patients with severe TBI being treated in ICUs were randomized to either the pressure-monitoring group (used a protocol for monitoring intraparenchymal ICP) or the imaging–clinical examination group. (used a protocol based on imaging and clinical examination). **Results**: There was no significant between-group difference in the primary outcome, which was a combination of survival time, impaired consciousness, and functional status at 3 mo and 6 mo and neuropsychological status at 6 mo. Serious adverse events were similar in the two groups. **Conclusions**: Care focused on ICP monitoring is no better than care based on imaging and clinical examination in patients with severe TBI.
POLAR	JAMA 2018;320(21):2211-2220	**Title**: Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients With Severe Traumatic Brain Injury: The POLAR Randomized Clinical Trial **Purpose**: To assess the effect of early sustained prophylactic hypothermia versus normothermic management in patients with severe TBI. **Methods**: 511 patients with severe TBI were randomized to receive either prophylactic hypothermia or normothermic management. Prophylactic hypothermia involved temperatures between 33-35°C for ≥ 72 h and ≤ 7 d. **Results**: Favourable outcomes (Glasgow Outcome Scale-Extended score, 5-8) 6 months post-injury were present in 48.8% and 49.1% of the hypothermia and normothermia group, respectively (risk difference, 0.4% (95% CI, -9.4% to 8.7%); relative risk with hypothermia, 0.99 (95% CI, 0.82-1.19); P=0.94). **Conclusions**: Compared with normothermic management, early prophylactic hypothermia did not improve neurologic outcomes at 6 mo in those with severe TBI.

Trial Name	Reference	Clinical Trial Details
PEDIATRIC NEUROSURGERY		
Shunt Design Trial	Neurosurgery 1998;43:294-304	**Title**: Randomized Trial of Cerebrospinal Fluid Shunt Valve Design in Pediatric Hydrocephalus **Purpose:** To compare treatment failure rates of the Delta valve and the Orbis-Sigma valve (both designed to limit excess flow) to the standard differential-pressure valves. **Methods:** 344 hydrocephalic children undergoing their first CSF shunt insertion were randomized to receive one of three valves: standard differential-pressure valve, a Delta valve, or an Orbis-Sigma valve. Shunt failure was defined as resulting from either shunt obstruction, overdrainage, loculations of the cerebral ventricles, or infection. **Results:** 61% were shunt failure-free at 1 yr and 47% at 2 years, with a median shunt failure-free duration of 656 d. There was no difference in shunt failure-free duration among the three valves (P=0.24). **Conclusions: The**re is no significant difference in the rate of CSF shunt failure among shunts with different valve types for pediatric hydrocephalus.
Endoscopic third ventriculostomy vs. cerebrospinal fluid shunt in the treatment of hydrocephalus in children: a propensity score-adjusted analysis	Neurosurgery 2010;67(3):588-593	**Title**: Endoscopic Third Ventriculostomy vs. Cerebrospinal Fluid Shunt in the Treatment of Hydrocephalus in Children: a Propensity Score-adjusted Analysis **Purpose:** To determine whether endoscopic third ventriculostomy (ETV) survival is superior to shunt survival in the treatment of hydrocephalus in children. **Methods:** Analysis of a cohort of children with newly diagnosed hydrocephalus treated with ETV or shunt. Results: The relative risk of ETV failure is initially higher than that for shunt, but after about 3 mo, the relative risk becomes progressively lower for ETV. **Conclusions:** After the initial early period, patients could have a long-term survival benefit with ETV compared to shunt.
FUNCTIONAL SURGERY		
EARLYSTIM	NEJM 2013; 368:610-622	**Title**: Neurostimulation for Parkinson's Disease with Early Motor Complications **Purpose**: To assess whether neurostimulation would be beneficial in the treatment of earlier stage Parkinson's disease. **Methods**: Patients with early-stage Parkinson's disease were randomized to neurostimulation plus medical therapy or medical therapy alone. The primary endpoint was quality of life (PDQ-39 summary index). **Results**: The quality of life in the neurostimulation group improved by 7.8 points compared to a worsening of quality of life by 0.2 in the medical-therapy group (P=0.002). Neurostimulation provided benefit in terms of motor disability, activities of daily living, levodopa-induced motor complications, and time with good mobility and no dyskinesia. Serious adverse events related to surgery occurred in 17.7% of patients. **Conclusions**: Neurostimulation was superior to medical therapy for the treatment of early stage Parkinson's disease.
A randomized, controlled trial of surgery for temporal-lobe epilepsy	NEJM 2001;345(5):311-318	**Title**: A Randomized, Controlled Trial of Surgery for Temporal-lobe Epilepsy **Purpose**: To assess the efficacy and safety of surgery for temporal-lobe epilepsy. **Methods**: 80 patients with temporal-lobe epilepsy were randomized to either surgery or treatment with antiepileptic drugs for 1 yr. The primary outcome was absence of seizures that impair awareness of self and surroundings. **Results**: 58% of patients in the surgery-group were free of seizures impairing awareness compared to 8% in the medical group (P<0.001). Compared to the medical group, patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life (P<0.001). **Conclusions**: In temporal lobe epilepsy, surgery is superior to prolonged medical therapy in reducing seizures.
PROCESS	Pain 2007;132:179-188	**Title**: Spinal Cord Stimulation versus Conventional Medical Management for Neuropathic Pain: a Multicentre Randomised Controlled Trial in Patients with Failed Back Surgery Syndrome **Purpose**: To determine whether spinal cord stimulation (SCS) is an effective therapy in addition to conventional medical management (CMM) in patients with neuropathic pain secondary to failed back surgery syndrome (FBSS). **Methods**: 100 FBSS patients with predominant leg pain of neuropathic radicular origin were randomized to the SCS group (receive spinal cord stimulation plus conventional medical management) or CMM group (conventional medical management alone for at least 6 mo). **Results**: Significantly more patients in the SCS-group achieved 50% or more pain relief in the legs compared to the CMM-group (48% vs. 9%, P<0.001). The SCS-group experienced improved leg and back pain relief, quality of life, and functional capacity, and greater treatment satisfaction compared to the CMM-group (P≤0.05 for all comparisons). At 12 mo, 32% of SCS patients experienced device-related complications. **Conclusions**: Compared to medical management, SCS provides superior pain relief and greater improvements to quality of life in patients with neuropathic leg pain of radicular origin secondary to FBSS.
SPINE SURGERY		
Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial	Lancet 2005; 366(9486):643-648	**Title**: Direct Decompressive Surgical Resection in the Treatment of Spinal Cord Compression caused by Metastatic Cancer: A Randomised Trial **Purpose:** To evaluate the role of direct decompressive surgery in the treatment of spinal cord compression due to metastatic cancer. **Methods:** 101 patients with spinal cord compression due to metastatic cancer were randomly assigned to either treatment with surgery and XRT or treatment with XRT alone. **Results:** More patients in the surgery group (84%) were able to walk after treatment compared to those who received XRT alone (57%) (odds ratio 6.2 (95% CI 2.0-19.8) P=0.001). **Conclusions:** For patients with spinal cord compression secondary to metastatic cancer, direct decompressive surgery followed by XRT is superior to treatment with XRT alone.
SPORT: Surgical vs. Non-Operative Treatment for Lumbar Disc Herniation	Spine 2014;39(1):3-16	**Title**: Surgical vs. Non-Operative Treatment for Lumbar Disc Herniation: Eight-Year Results for the Spine Patient Outcomes Research Trial (SPORT) **Purpose**: To assess the 8-yr outcomes of surgery vs. non-operative care in patients with imaging-confirmed lumbar intervertebral disc herniation **Methods**: In the RCT arm of the study, 501 patients with imaging-confirmed lumbar disc herniation were randomized to open discectomy vs. standard non-operative management. **Results**: Surgery was superior in intention-to-treat analysis for sciatica severity (P=0.005), patient satisfaction (P=0.013), and self-rated improvement (P=0.013) at 8 yr follow-up. Improvements in pain, physical function, and disability were only seen in an as-treated analysis due to significant non-adherence to treatment assignment. **Conclusion**: Patients who are carefully selected for surgical intervention show greater symptom improvement compared to non-operative management.

Trial Name	Reference	Clinical Trial Details
SPORT: Long-Term Outcomes of Lumbar Spinal Stenosis	Spine 2015;40(2):63-76	**Title**: Long-Term Outcomes of Lumbar Spinal Stenosis: Eight Year Results of the Spine Patient Outcomes Research Trial (SPORT) **Purpose**: To compare 8-year outcomes of surgery vs. nonoperative care for symptomatic lumbar spinal stenosis. **Methods**: In the RCT arm of the study, 289 patients were randomized to decompressive laminectomy (n=138) or standard non-operative care (n=151). **Results**: intention-to-treat analyses showed no difference in pain, physical function, and disability outcome measures, because 52% randomized to non-operative management had undergone surgery at 8 yr. As-treated analyses showed early benefits for surgery until 4 yr, however effects in primary outcomes converged between 5-8 yr. **Conclusion**: Decompressive laminectomy for symptomatic spinal stenosis may show diminishing symptomatic benefits beyond 4 yr.
STASCIS	PLoS ONE 2012;7:e32037	**Title**: Early vs. Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) **Purpose**: This study sought to determine the relative effectiveness of early (<24 h after injury) vs. late (≥24 h after injury) decompressive surgery following a traumatic cervical SCI. **Methods**: A prospective cohort study completed in 2002-2009 involving 6 North American institutions. Participants were 16-80 yr with a cervical SCI. Outcomes evaluated were changes in American Spinal Injury Association Impairment Scale (AIS) grade at 6 mo follow-up, complication rates, and mortality. **Results**: Of 313 participants enrolled, 182 underwent early surgery and 131 underwent late surgery. 222 participants were available for follow-up at 6 mo. The odds of ≥ 2 grade AIS improvement were greater for those who had early surgery compared to those with late surgery (OR 2.83, 95% CI 1.10, 7.28) after adjusting for preoperative neurological status and steroid administration. Mortality was observed for each group during the first 30 d post injury, only 1 mortality occurred in both of the surgical groups. No statistically significant differences were observed for complications (P=0.21). **Conclusion**: Early decompression surgery following a SCI is safe and associated with higher AIS improvement at 6 mo following injury.
Effect of Ventral vs. Dorsal Spinal Surgery on Patient-Reported Physical Functioning in Patients With Cervical Spondylotic Myelopathy: A Randomized Clinical Trial	JAMA 2021;325(10):942-951	**Title**: Effect of Ventral vs. Dorsal Spinal Surgery on Patient-Reported Physical Functioning in Patients With Cervical Spondylotic Myelopathy: A Randomized Clinical Trial **Purpose**: To compare ventral surgery to dorsal surgery for cervical spondylotic myelopathy in improving patient-reporting physical functioning 1 yr post-injury. **Methods**: 163 patients with multilevel cervical spondylotic myelopathy were randomized to undergo either ventral or dorsal surgery. Physical functioning at 1 yr was reported using the Short Form 36 physical component summary score. **Results**: Mean improvement in patient-reported physical functioning at 1 yr was not significantly different between ventral surgery (5.9 points) and dorsal surgery (6.2 points) (estimated mean difference, 0.3; 95% CI, -2.6 to 3.1; P=0.86). **Conclusions**: In patients with cervical spondylotic myelopathy, ventral surgery was not superior in improving patient-reported physical functioning at 1 yr compared to dorsal surgery.
CSM-Protect	Lancet 2021;20(2);98-106	**Title**: Safety and Efficacy of Riluzole in Patients Undergoing Decompressive Surgery for Degenerative Cervical Myelopathy (CSM-Protect): A Multicentre, Double-blind, Placebo-controlled, Randomised, Phase 3 Trial **Purpose**: To assess whether riluzole improves outcomes for patients with degenerative cervical myelopathy undergoing decompression surgery. **Methods**: 290 patients undergoing decompression surgery randomly received either oral riluzole (50 mg twice a day for 14 d before surgery and then for 28 d after surgery) or placebo. **Results**: There was no difference in the change in modified Japanese Orthopedic Association score between the two groups (difference -0.38 points, -0.90 to 0.13; p=0.14). **Conclusions**: In patients with degenerative cervical myelopathy, adjuvant treatment with riluzole did not enhance functional recovery beyond decompressive surgery.
The influence of timing of surgical decompression for acute spinal cord injury: a pooled analysis of individual patient data	Lancet Neurology 2021;20(2):117-26	**Title:** The Influence of Timing of Surgical Decompression for Acute Spinal Cord Injury: A Pooled Analysis of Individual Patient Data **Purpose:** To evaluate the effect of timing of decompressive surgery for acute SCI on long-term neurological outcomes. **Methods:** Pooled analysis of individual patient data derived from four independent, prospective, multicentre data sources, including data from December, 1991 to March, 2017. **Results:** Patients who underwent early surgical decompression (n=528) experienced greater recovery than patients who had late decompression surgery (n=1020) at 1 year after spinal injury; total motor scores improved by 23.7 points (95% CI 19.2–28.2) in the early surgery group versus 19.7 points (15.3–24.0) in the late surgery group (MD 4.0 points (1.7–6.3); p=0.0006), light touch scores improved by 19.0 points (15.1–23.0) vs. 14.8 points (11.2–18.4; MD 4.3 (1.6–7.0); p=0.0021), and pin prick scores improved by 18.3 points (13.7–22.9) versus 14.2 points (9.8–18.6; MD 4.0 (1.5–6.6); p=0.0020). **Conclusions:** Surgical decompression within 24 h of acute SCI is associated with improved sensorimotor recovery. The first 24–36 h after injury appears to represent a crucial time window to achieve optimal neurological recovery with decompressive surgery following acute SCI.

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OB Obstetrics

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Acronyms

AC	abdominal circumference
ACOG	American College of Obstetricians and Gynecologists
AFI	amniotic fluid index
AFLP	acute fatty liver of pregnancy
AFV	amniotic fluid volume
AP	anteroposterior
APGAR	appearance, pulse, grimace, activity, and respiration
aPTT	activated partial thromboplastin time
APS	antiphospholipid antibody syndrome
ARDS	acute respiratory distress syndrome
BPP	biophysical profile
CD	caesarean delivery
CMV	cytomegalovirus
CPD	cephalopelvic disproportion
CTG	cardiotocography
CVS	chorionic villus sampling
D&C	dilation and curettage
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ECV	external cephalic version
EDD	estimated date of delivery
EFM	electronic fetal monitoring
eFTS	enhanced first trimester screen
EFW	estimated fetal weight
FDP	fibrin degradation products
FHR	fetal heart rate
FISH	fluorescence in situ hybridization
FL	femur length
FM	fetal movement
FPG	fasting plasma glucose
FTS	first trimester screen
GA	gestational age
GBS	Group B Streptococcus
GDM	gestational diabetes mellitus
GPA	gravida para abortus
GTN	gestational trophoblastic neoplasia
HBIG	hepatitis B immunoglobulin
HC	head circumference
HELLP	hemolysis, elevated liver enzymes, and low platelets
IMM	intramyometrial
IOL	induction of labour
IPS	integrated prenatal screen
ITP	immune thrombocytopenic purpura
IUFD	intrauterine fetal demise
IUGR	intrauterine growth restriction
IVF	*in vitro* fertilization
IVH	intraventricular hemorrhage
L/S	lecithin-sphingomyelin ratio
LLDP	left lateral decubitus position
LMP	last menstrual period
LMWH	low molecular weight heparin
MSAFP	maternal serum α-fetoprotein
MSS	maternal serum screening
MTX	methotrexate
NIPT	non-invasive prenatal testing
NPO	nil per os - nothing by mouth
NST	non-stress test
NT	nuchal translucency
NTD	neural tube defects
OA	occiput anterior
OCP	oral contraceptive pill
OGCT	oral glucose challenge test
OGTT	oral glucose tolerance test
ONTD	open neural tube defect
OP	occiput posterior
OT	occiput transverse
PAPP-A	pregnancy-associated plasma protein A
PG	plasma glucose
PPD	postpartum depression
PPH	postpartum hemorrhage
PPROM	preterm prelabour rupture of membranes
PROM	prelabour rupture of membranes
PTL	preterm labour
QF-PCR	quantitative fluorescence-polymerase chain reaction
RDS	respiratory distress syndrome
RhIG	Rh immune globulin
ROM	rupture of membranes
SFH	symphysis fundal height
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SOGC	Society of Obstetricians and Gynaecologists of Canada
SVD	spontaneous vaginal delivery
T1	first trimester
T2	second trimester
T3	third trimester
TENS	transcutaneous electrical nerve stimulation
TOLAC	trial of labour after Caesarean
TPN	total parenteral nutrition
TTP	thrombotic thrombocytopenic purpura
TVUS	transvaginal ultrasound
V/Q	ventilation/perfusion lung scan
VBAC	vaginal birth after caesarean
VWD	von Willebrand disease
VTE	venous thromboembolism

Basic Anatomy Review

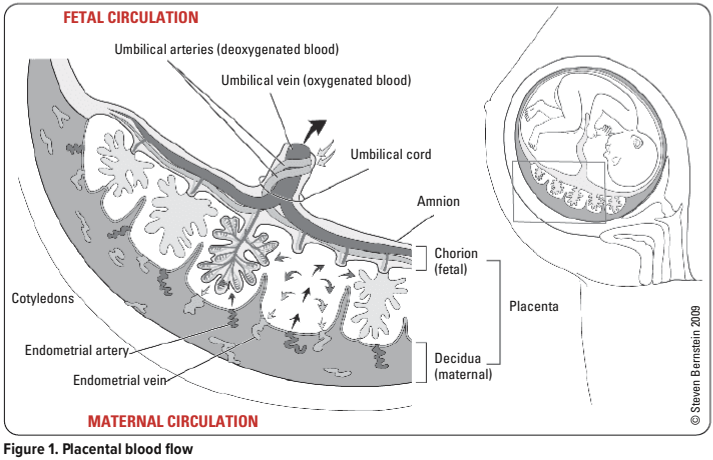

Figure 1. Placental blood flow

Placenta

- 1° site of nutrient and gas exchange between mother and fetus
- discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- produces hormones such as progesterone, placental lactogen, estrogen, relaxin, β-hCG, and infant growth factors
- poor implantation can lead to spontaneous abortion
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see *Antepartum Hemorrhage, OB14*)

Pregnancy

Diagnosis of Pregnancy

History

- symptoms: amenorrhea, N/V, breast tenderness, urinary frequency, and fatigue
- for obstetrical and gynecological history note: year, location, mode of delivery, duration of labour, fetal sex, GA, birth weight, and complications of every pregnancy; organize into GTPAL format, LMP, length of menstrual cycle, and use of contraception
  - gravidity (G)
    - G: total number of pregnancies of any gestation (multiple gestation=one pregnancy)
      - includes current pregnancy, abortions, ectopic pregnancies, and hydatidiform moles
  - parity (TPAL)
    - T: number of term deliveries (>37 wk GA)
    - P: number of preterm deliveries (20+0 to 36+6 wk GA)
    - A: number of abortions and ectopic pregnancies (ending <20 wk GA)
      - induced (therapeutic) and spontaneous (miscarriage)
    - L: number of living children

Be conscious of the use of gendered language when providing reproductive care to transgender male and gender-diverse patients. Discuss with each patient the terminology they are most comfortable using in order to avoid gender dysphoria throughout pregnancy care

Physical Signs

- uterine and abdominal enlargement
- breast engorgement, areola darkening, and prominent vascular patterns
- Goodell's sign: softening of the cervix (4-6 wk GA)
- Chadwick's sign: bluish discolouration of the cervix and vagina due to pelvic vasculature engorgement (6 wk GA)
- Hegar's sign: softening of the cervical isthmus (6-8 wk GA)

Establishing the desirability of pregnancy in a patient with suspected or confirmed pregnancy informs the construction of an appropriate management plan

Investigations

- β-hCG: peptide hormone composed of β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy
  - positive in serum 9 d postconception, positive in urine 28 d after 1st day of LMP
  - plasma levels double q48h in a normally developing pregnancy from the time it becomes detectable until it peaks at ~100000 (approximately at 8-10 wk GA) then falls but continues to be measurable until delivery
  - levels less than expected can suggest ectopic pregnancy, miscarriage, inaccurate dates, but found in some normal pregnancies
  - levels greater than expected can suggest multiple gestation, molar pregnancy, trisomy 21, inaccurate dates, some normal pregnancies, or kidney disease (slower clearance)
- U/S:
  - transvaginal
    - 5 wk GA: gestational sac visible
    - 6 wk GA: fetal pole visible
    - 6-8 wk GA: fetal heart activity visible (FHR visible after 6 wk GA on TVUS)
  - transabdominal
    - 6-8 wk GA: intrauterine pregnancy visible

β-hCG Rule of 10s
10 IU at time of missed menses
100000 IU at 10 wk GA (peak)
10000 IU at term

Trimesters
T1: 1-14 wk GA
T2: 14-28 wk GA
T3: 28-42 wk GA
Normal pregnancy term: 37-42 wk GA

Maternal Physiologic Adaptations to Pregnancy

Table 1. Physiologic Changes During Pregnancy

	Changes
Skin	Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation) Proliferation of skin tags Spider angiomas Palmar erythema due to increased estrogen Striae gravidarum due to connective tissue changes
Cardiovascular	Hyper-dynamic circulation Increased cardiac output, heart rate, and blood volume Decreased blood pressure: decreased PVR due to progesterone's effect on vascular smooth muscle and decreased venous return from enlarging uterus compressing IVC and pelvic veins Increased venous pressure leads to risk of varicose veins, hemorrhoids, and leg edema
Hematologic	Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit Increased leukocyte count but impaired function leads to improvement in some autoimmune diseases Decreased total protein largely due to dilution and decreased serum albumin Gestational thrombocytopenia: mild (platelets >70000/μL) and asymptomatic, normalizes within 2-12 wk following delivery Hypercoagulable state: increased risk of DVT and PE but also decreased bleeding at delivery

PVR – pulmonary vascular resistance; IVC – inferior vena cava; FEV1 – forced expiratory volume in 1 second; CO – cardiac output; GFR – glomerular filtration rate; BUN – blood urea nitrogen; GERD – gastroesophageal reflux disease

Table 1. Physiologic Changes During Pregnancy

	Changes
Respiratory	Increased incidence of nasal congestion Increased O_2 consumption to meet increased metabolic requirements Elevated diaphragm (i.e. appears more "barrel-chested") Increased minute ventilation leads to decreased CO_2 resulting in mild respiratory alkalosis that helps CO_2 diffuse across the placenta from fetal to maternal circulation Decreased total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) No change in vital capacity (VC) and FEV_1
Gastrointestinal	Increased incidence of gallstones due to progesterone causing increased gallbladder stasis Constipation due to progesterone causing decreased GI motility and hemorrhoids as a result of constipation and increased intra-abdominal pressure Predisposition to GERD due to reduced lower esophageal sphincter tone (progesterone), delayed gastric emptying, and compression by gravid uterus
Genitourinary	Increased urinary frequency due to increased total urinary output Increased incidence of UTI and pyelonephritis due to urinary stasis (see *Urinary Tract Infection, OB31*) Glycosuria can be physiologic especially in T3 due to renal plasma flow increase exceeding that of GFR preventing reabsorption of glucose as per the non-pregnant state; consider testing for GDM if noted in first 2 trimesters Ureteric and renal pelvis dilatation (R>L) due to progesterone-induced smooth muscle relaxation and uterine enlargement Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 35-44 mmol/L), uric acid, and BUN
Neurologic	Increased incidence of carpal tunnel syndrome, sciatica, and Bell's palsy
Endocrine	Thyroid: moderate enlargement (not clinically detectable) and increased basal metabolic rate Increased total thyroxine and thyroxine binding globulin (TBG) Normal free thyroxine index and TSH levels Physiologic suppression of TSH in T1 is common due to cross-reactivity of HCG to TSH receptors Pituitary: enlargement of the pituitary gland due to lactotroph hyperplasia, increasing circulating prolactin levels Adrenal: increased maternal cortisol throughout pregnancy (total and free) Calcium: decreased total maternal Ca^{2+} due to decreased albumin Free ionized Ca^{2++} (i.e. active) proportion remains the same due to decreased parathyroid hormone (PTH), resulting in increased bone resorption and gut absorption, and increased bone turnover (but no loss of bone density due to estrogen inhibition) (see *Diabetes Mellitus, OB28*)

PVR – pulmonary vascular resistance; IVC – inferior vena cava; FEV1 – forced expiratory volume in 1 second; CO – cardiac output; GFR – glomerular filtration rate; BUN – blood urea nitrogen; GERD – gastroesophageal reflux disease

Antepartum Care

- can be provided by an obstetrician, family physician, midwife, or multidisciplinary team (based on patient preference and risk factors)

Preconception Counselling

- 3-8 wk GA is a critical period of organogenesis, so early preparation is vital
- PMHx: optimize medical conditions and review medications prior to pregnancy (see *Medical Complications of Pregnancy, OB28* and *Medications, OB13*)
- supplementation
  - folic acid: see *Counselling of the Pregnant Patient, OB11* and *Medical Complications of Pregnancy, OB28*
- prenatal vitamins (PNV), consider iron supplementation in T2 and T3 (earlier in cases of iron deficiency anemia)
- lifestyle/social risk factors should be reviewed: smoking, alcohol (abstinence should be encouraged leading up to and during pregnancy), substance use (can lead to intellectual deficits and behavioural challenges in childhood), domestic violence, occupational risks, poor social support, balanced nutrition, and physical fitness (see Family Medicine)
- medications: discuss teratogenicity of medications so they may be adjusted, replaced, or stopped if necessary
- infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV, TB testing based on travel and working in healthcare, history of varicella or vaccination, and parvovirus immunity if exposed to small children
- genetic testing as appropriate for high-risk groups (see *Prenatal Screening, Table 2, OB7*); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay, birth anomalies, genetic diseases, and consanguinity

Initial Prenatal Visit

- usually within 8-12 wk of the 1st day of LMP or earlier if <20 or >35 y/o, bleeding, very nauseous, or other risk factors present

History

- GA by dates from the 1st day of LMP

Family physicians and midwives can consider OB consultation for conditions including:

- Insulin-dependent GDM
- TOLAC
- Multiple gestation
- Malpresentation
- Active antepartum hemorrhage
- PTL/PPROM
- Failure to progress/descend
- Induction/augmentation if high-risk
- Tears: 3rd or 4th degree
- Retained placenta
- IUGR
- Postpartum hemorrhage

Note: Guidelines vary by institution and by provincial midwifery colleges

Advise all patients capable of becoming pregnant to supplement their diet with 0.4 mg/d of folic acid (CTFPHC Grade II-2-A Evidence)

- Naegele's rule: 1st day of LMP + 1 yr + 7 d – 3 mo
- e.g. LMP = 1 Apr 2021, EDD = 8 Jan 2022 (modify if cycle not 28 d by adding number of d >28 or subtracting number of d <28)
- EDD by LMP not reliable if irregular menstrual cycle, or if patient unsure of the LMP

- dating U/S is the best parameter for determining GA and should be offered at 8-12 wk GA
- history of present pregnancy (e.g. bleeding, N/V) and all previous pregnancies
- past medical, surgical, and gynaecological history
- prescription and non-prescription medications
- family history: diabetes, hypertension, thyroid disease, mental health issues, genetic diseases, birth defects, multiple gestation, and consanguinity
- social history: smoking, alcohol, and substance use
- intimate partner violence screening: look for bruising, improbable injury, depression, late prenatal care (presenting at T2 or T3), missed prenatal visits, and/or appointments cancelled on short notice (see Family Medicine, *Intimate Partner Violence*, FM29)

Physical Exam
- complete physical exam to obtain baseline patient information – BP and weight important for interpreting subsequent changes
- BMI for risk stratification (risk of DVT, GDM, and preeclampsia all increase with greater BMI)

Investigations
- blood work
  - CBC, blood group and Rh status, antibody screen, and infection screening as per preconception counselling
- urine routine & microscopic, midstream urine C&S
  - screen for bacteriuria and proteinuria
- pelvic exam
  - Pap smear (only if required according to patient history and provincial screening guidelines), cervical or urine PCR for *N. gonorrhoeae* (GC) and *C. trachomatis* (CT)

In history of previous pregnancies, **ALWAYS** ask:
GTPAL
Year of delivery
Fetal sex
Birth weight
Gestational age
Mode of delivery
Length of labour
Complications

Ask everyone about abuse – not just those whose situations raise suspicion of abuse AND ask as early as possible in pregnancy

Estimated Date of Delivery Determination
- By LMP if menses regular, given patient reliable historian
- By T1 U/S, the most accurate method of establishing GA up to 13+6/7 wk GA
- By embryo age and date of transfer if IVF
- Changes to the EDD must be documented and discussed with the patient
- Pregnancy without U/S confirming or revising the EDD prior to 22+0/7 wk GA is considered sub-optimally dated

Nausea and Vomiting

Epidemiology
- affects 50-90% of pregnant patients
- often limited to T1 but may persist beyond this

Management
- rule out other causes of N/V especially if refractory to initial therapy
- weigh frequently, assess level of hydration, and test urine for ketones
- non-pharmacological
  - frequent small meals (bland, dry, salty are better tolerated), encourage any safe, appealing foods
  - electrolyte oral solutions (Pedialyte®, Gatorade®)
  - stop prenatal vitamins and if T1, substitute with folic acid or adult/children's vitamins that are low in iron
  - increase sleep/rest
  - ginger (maximum 1000 mg/d)
  - acupuncture, acupressure, and mindfulness-based cognitive therapy
- pharmacological
  - first line: pyridoxine (vitamin B_6) monotherapy or doxylamine/pyridoxine (Diclectin®) combination 4 tablets PO daily (1 q AM, 1 q lunch, and 2 qhs) up to maximum of 8 tablets/d
  - H1 receptor antagonists should be considered for acute or chronic episodes of N/V in pregnancy
  - metoclopramide and phenothiazines can be used as an adjunctive therapy for severe N/V in pregnancy
  - ondansetron if severe N/V and other anti-emetics have failed
  - consider use of acid-reducing medications as adjunctive therapy (e.g. antacids, H2 blockers, proton pump inhibitors)

Hyperemesis Gravidarum

Definition
- intractable N/V, usually presents in T1 then diminishes; occasionally persists throughout pregnancy

Epidemiology
- affects ~1% of pregnancies

Etiology
- multifactorial with hormonal, immunologic, and psychological components
- rapidly rising β-hCG ± estrogen levels may be implicated

Investigations
- rule out systemic causes: GI, pyelonephritis, thyrotoxicosis
- rule out other obstetrical causes: multiple gestation, GTN
- CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
- U/S

Management
- thiamine supplementation may be indicated
- non-pharmacological (see *Nausea and Vomiting, OB5*)
- pharmacological options
  - consider homecare with IV fluids and parenteral anti-emetics, and/or hospitalization
  - doxylamine/pyridoxine (for dosage, see *Nausea and Vomiting, OB5*)
  - dimenhydrinate can be safely used as an adjunct to Diclectin® (1 suppository BID or 25-50 mg PO QID)
  - other adjuncts: hydroxyzine, pyridoxine, phenothiazine, or metoclopramide
  - also consider: ondansetron or methylprednisolone (avoid steroids in T1 due to increased risk of oral clefting)
  - if severe: admit to hospital, NPO initially then small frequent meals; correct hypovolemia, electrolyte disturbance, and ketosis; TPN (if very severe) to reverse catabolic state

Complications
- maternal
  - dehydration, electrolyte, and acid-base disturbances
  - Mallory-Weiss tear
  - Wernicke's encephalopathy, if protracted course
  - death
- fetal: usually none, IUGR is 15x more common in patients losing >5% of pre-pregnancy weight

Subsequent Prenatal Visits

Timing
- for uncomplicated pregnancies, SOGC recommends q4-6 wk GA until 30 wk GA, q2-3 wk from 30 wk GA, and q1-2 wk from 36 wk GA until delivery

Assess at Every Visit
- estimated GA
- history: FM, vaginal bleeding, leaking, cramping, questions, and/or concerns
- physical exam: BP, weight gain, SFH, Leopold's maneuvers (T3) to determine the lie, and presentation of fetus
- investigations: urinalysis for proteinuria in high-risk women (hypertensive patients); FHR starting at 10-12 wk GA using Doppler U/S

Leopold's Maneuvers
- performed after 30-32 wk GA
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver: to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

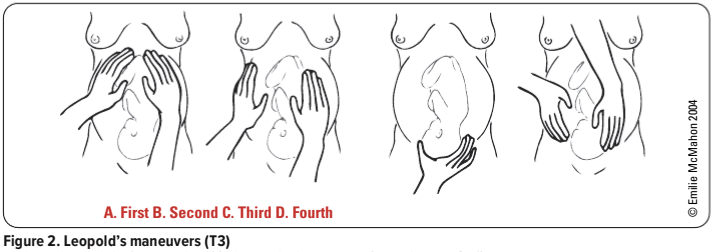

Figure 2. Leopold's maneuvers (T3)
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Symphysis Fundal Height (SFH)

12 wk GA	Uterine fundus at pubic symphysis
16 wk GA	Fundus halfway from pubic symphysis to umbilicus
20 wk GA	Fundus at umbilicus
20-36 wk GA	SFH should be within 2 cm of GA

SFH < Dates
- Date miscalculation
- IUGR
- Fetal demise
- Oligohydramnios
- Early engagement
- Transverse lie

SFH > Dates
- Date miscalculation
- Multiple gestation
- Polyhydramnios
- Large for GA (familial, DM)
- Fibroids

Prenatal Screening and Diagnostic Tests

Screening Tests

- testing should only occur following counselling and with informed consent from the patient

Table 2. High-Risk Population Screening Tests

Disease (Inheritance)	Population(s) at Risk	Screening Test(s)
Thalassemia (AR)	Individuals from these regions: Mediterranean, South East Asia, Western Pacific, Africa, Middle East, Caribbean, South America	CBC (Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCH)), Hb electrophoresis, or HPLC
Sickle Cell (AR)	Individuals from these regions: Africa, Caribbean, Mediterranean, Middle East, India, South America	CBC (MCV and MCH), Hb electrophoresis, or HPLC
Cystic Fibrosis (CF) (AR)	Family history of CF in patient or partner or medical condition linked to CF like male infertility	CFTR gene DNA analysis
Tay Sachs Disease (AR)	Ashkenazi Jewish*, French Canadians, Cajun	Enzyme assay HEXA or DNA analysis HEXA gene
Fragile X Syndrome (X-linked)	Family history – confirmed or suspected	DNA analysis: FMR-1 gene

AR = autosomal recessive; HEXA = hexosaminidase A; HPLC = high performance liquid chromatography
*If both partners are Ashkenazi Jewish, test for Canavan disease and Familial Dysautonomia (FD); if family history of a specific condition, look for carrier status: e.g. Gaucher disease, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners are positive, refer for genetic counselling.

Table 3. Gestation-Dependent Screening Investigations

Gestational Age (wk)	Investigations	Details
Preimplantation	Preimplantation genetic testing for aneuploidy, Preimplantation genetic testing for monogenic (single-gene) disorders, Preimplantation genetic testing for structural rearrangements	All require IVF
8-12	Dating U/S, possible Pap smear, chlamydia/gonorrhea testing, urine C&S (detect asymptomatic bacteriuria), HIV, VDRL, HBsAg, Rubella IgG, Parvovirus IgM if symptomatic or IgG if high-risk (small child at home or daycare worker/ primary teacher), Varicella IgG if no history of disease/ immunization, CBC, blood group and screen	
>10	NIPT	Measures cell-free fetal DNA in maternal circulation
10-12	CVS	Diagnostic test, NOT screening
11-13+3	eFTS	Combination of nuchal translucency US and bloodwork (bhcg, PAPP-A, Placental growth factor, MSAFP)
11-13+3	NT	Ultrasound to measure nuchal translucency
15-16 to term	Amniocentesis	Diagnostic test, NOT screening
15-20	MSS	Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A
18-20 to term	FM (quickening)	
18-20	U/S for fetal size, anatomy assessment, and placental location	
24-28	Gestational Diabetes Screen OGCT 50 g	See *Diabetes Mellitus, OB28*
28	Repeat CBC, ferritin, group and screen, RhIG for all Rh-negative women	
35-37	GBS screen	See *Early-Onset Group B Streptococcus, OB30*
6 wk postpartum	Discuss contraception, menses, breastfeeding, depression, mental health, and support Physical exam: breast exam, pelvic exam including Pap smear (only if due), scar assessment (perineum or CD)	

MSS is also referred to as Triple Screen; if Inhibin A is also tested, it is referred to as Quadruple Screen
Can consider ordering AFP to screen for ONTDs in women with BMI >40

Routine T2 U/S at 18-22 wk GA Helps to Determine:

- Number of fetuses
- GA (if no prior U/S)
- Location of placenta
- Length of cervix
- Fetal structural anomalies

DDx of Increased MSAFP

- Incorrect GA
- >1 fetus (e.g. twins)
- Fetal loss
- ONTD
- Abdominal wall defects (e.g. omphalocele)

ULTRASOUND SCREENING

- 8-12 wk GA: dating U/S (most accurate form of pregnancy dating)
  - measurement of crown-rump length (margin of error: ± 5 d)
  - EDD should be based on T1 U/S if available
- 11-13+3 wk GA: U/S for NT
  - measures the amount of fluid behind the neck of the fetus
  - early screen for trisomy 21 (may also detect cardiac anomalies and other aneuploidies like Turner syndrome)
  - NT measurement is necessary for the eFTS
- 18-20 wk GA: growth and anatomy U/S (margin of error: ± 10 d)
  - earlier or subsequent U/S performed when medically indicated

NON-INVASIVE PRENATAL TESTING (NIPT)

- analyze maternal blood for circulating cell-free fetal DNA (ccffDNA) at 10 wk GA onwards. Requires dating U/S for accuracy

Advantages

- increased accuracy (high detection rate (DR), low false positive rate (FPR))
  - trisomy 21 (DR 99%, FPR 0.1%), highly sensitive
  - trisomy 18 (DR 96%, FPR 0.1%)
  - trisomy 13 (DR 91%, FPR 0.1%)
  - Turner syndrome (DR 90%, FPR 0.2%)
  - other disorders (DiGeorge syndrome, Cri Du Chat syndrome, Prader-Willi syndrome, Angelman syndrome, XY disorders)
- results available within 1-2 wk allowing earlier CVS at 10-12 wk GA relative to amniocentesis at 15 wk GA

Disadvantages

- does not screen for ONTD
- not covered by most provincial health insurance systems
- need to confirm results with invasive testing (it is a screening test, not a diagnostic test)
- obtaining a result depends on sufficient fetal fraction (affected by the GA, maternal obesity, and presence of a chromosome aneuploidy in either the placenta or the mother)
- does not test for all aneuploidies
- gives no result in 1-5% of cases (insufficient fetal fraction, more common with elevated BMI)

Table 4. Comparison of FTS, MSS, and IPSNIPT

eFTS	MSS	NIPT
11-14 wk GA	15-20 wk GA	10 wks onward
Risk estimate for 1. Trisomy 21 (Down syndrome): increased NT, increased β-hCG, decreased PAPP-A 2. Trisomy 18: increased NT, decreased PAPP-A Note: Useful when patient wants results within T1 more accurate estimate of trisomy 21 risk than MSS, sensitivity ~85% (when combined with age) 5% FPR Patients with positive screen should be offered CVS, amniocentesis, or NIPT (covered in some provinces, self-pay in others)	Risk estimate for 1. ONTD: increased MSAFP (sensitivity 80-90%) 2. Trisomy 21: decreased MSAFP, increased β-hCG, decreased μE3 (sensitivity 65%) 3. Trisomy 18: decreased MSAFP, decreased β-hCG, decreased μE3, decreased inhibin A (sensitivity 80%) Only offered alone if patient missed the time window for IPS or eFTS 8% baseline FPR for trisomy 21, lower for NTD and trisomy 18 Patients with positive screen should be offered U/S, amniocentesis, or NIPT (covered in some provinces, self-pay in others)	Risk estimate for trisomy 21 (DR 99%, FPR 0.1%), highly sensitive

Note: In twins, eFTS, MSS, and IPS are not applicable; screen with NT, NIPT for chromosomal abnormalities, and MSAFP for ONTDs

Diagnostic Tests

- diagnostic tests available:
  - amniocentesis
  - CVS

Indications

- age >35 yr (increased risk of chromosomal anomalies)
- risk factors in current pregnancy
- abnormal U/S
- abnormal prenatal screen (eFTS, MSS, or NIPT)
- past history/family history of:
  - chromosomal anomaly or genetic disease
  - either parent a known carrier of a genetic disorder or balanced translocation
  - consanguinity
  - >3 spontaneous abortions

AMNIOCENTESIS

- U/S-guided transabdominal extraction of amniotic fluid performed as early as 15 wk GA

Indications

- identification of genetic and chromosomal anomalies (15-16 wk GA) as per indications above
- confirmation of positive NIPT/eFTS/MSS
- positive eFTS/IPS/MSS
- assessment of fetal lung maturity (T3) via the L/S ratio
  - if >2:1, RDS is less likely to occur

Compared to CVS, amniocentesis has a higher accuracy of prenatal cytogenetic diagnosis (99.8% vs. 97.5%) and lower risk of spontaneous abortion (0.5% vs. 1-2%)

Advantages
- also screens for ONTD (acetylcholinesterase and amniotic AFP) – 96% accurate
- in women >40 yr, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- more accurate than CVS

Disadvantages
- 1/200 to 1/900 risk of procedure-related pregnancy loss, depending on local experience
- results take 14-28 d; QF-PCR or FISH can be done on chromosomes X, Y, 13, 18, 21, 22 to give preliminary results in 24 h; chromosomal microarray also readily available

Risk Factors for Neural Tube Defects

GRIMM
Genetics: family history of NTD (risk of having second child with NTD is increased to 2-5%), consanguinity, chromosomal (characteristic of trisomy 13, 18, and 21)
Race: Higher risk in Europeans and non-Hispanic whites than African Americans, 3-fold higher in Hispanics
Insufficient vitamins: zinc and folate
Maternal chronic disease (e.g. DM)
Maternal use of antiepileptic drugs

General population risk for NTD is 0.1%

CHORIONIC VILLUS SAMPLING
- biopsy of fetal-derived chorion using a transabdominal needle or transcervical catheter at 10-12 wk GA

Advantages
- enables pregnancy to be terminated earlier than with amniocentesis
- rapid karyotyping and biochemical assay within 48 h, including FISH analysis
- high sensitivity and specificity

Disadvantages
- 1% risk of procedure-related pregnancy loss
- does not screen for ONTD
- 1-2% incidence of genetic mosaicism "false negative" results

ISOIMMUNIZATION SCREENING

Definition
- isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigenic stimulation with RBC of another individual

Etiology
- maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
- anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
- risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16%
- sensitization routes
  - incompatible blood transfusions
  - previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy, trauma, abruption)
  - invasive procedures in pregnancy (e.g. prenatal genetic diagnosis, cerclage, D&C)
  - any type of abortion
  - labour and delivery
  - trauma (e.g. car accident, fall, etc.)

Rh Antibody Titre
A positive titre (≥1:16) indicates an increased risk of fetal hemolytic anemia

Investigations
- screening with indirect Coombs test at first visit for blood group, Rh status, and antibodies
- Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage by estimating volume of fetal blood volume that entered maternal circulation
- detailed U/S for hydrops fetalis
- middle cerebral artery Dopplers are done to assess degree of fetal anemia; if not available, bilirubin is measured by serial amniocentesis to assess the severity of hemolysis
- cordocentesis for fetal Hb should be used cautiously (not first-line)

Standard dose of 300 µg of Rhogam® sufficient for 30 mL of fetal blood. Give additional 10 µg of Rhogam® for every mL of fetal blood over 30 mL

Prophylaxis
- exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
- Rhogam® (120-300 µg) given to all Rh-negative and antibody screen negative patients in the following scenarios:
  - routinely at 28 wk GA (provides protection for ~12 wk)
  - within 72 h of the birth of a Rh-positive fetus
  - with any invasive procedure in pregnancy (CVS, amniocentesis)
  - as part of management of ectopic pregnancy
  - with miscarriage or therapeutic abortion
  - with an antepartum hemorrhage
  - with trauma
- Rhogam® 300 µg provides sufficient prophylaxis for 30 mL fetal Rh-positive whole blood
- a Kleihauer-Betke test or flow cytometry can be used to measure the relative quantity of fetal blood in maternal circulation to determine if additional Rhogam® is indicated (if >30 mL fetal blood)
- if Rh-negative and Ab screen positive, follow mother with serial monthly Ab titres throughout pregnancy + U/S ± serial amniocentesis as needed (Rhogam® has no benefit, as B cells/antibodies already in circulation)

Treatment
- falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
- intrauterine transfusion between 18-35 wk GA of O-negative packed RBCs may be required for severely affected fetus
- early delivery of the fetus for exchange transfusion following 35 wk GA

Complications
- anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, and/or ascites
- severe cases can lead to hydrops fetalis (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)

Fetal Surveillance

- patients will generally first notice FM ("quickening") at 18-20 wk GA in primigravidas; can occur 1-2 wk earlier in multigravidas; can occur 1-2 wk later if placenta is implanted on the anterior wall of uterus
- if there is concern about decreased FM, the patient is counselled to choose a time when the fetus is normally active to count movements (usually recommended after 26 wk GA)
- all high-risk patients should be advised to do FM counts
  - should experience ≥6 perceived movements in 2 h period
  - if there is a subjective decrease in FM, time how long it takes to feel 6 discrete movements (laying on the left in a quiet setting may facilitate feeling subtle movements)
  - if 6 movements take more than 2 h, further assessment is indicated, and patient should present to labour and delivery triage for assessment

DDx of Decreased Fetal Movements

DASH
Death of fetus
Amniotic fluid decreased
Sleep cycle of fetus
Hunger/Thirst

NON-STRESS TEST

Definition
- FHR tracing ≥20 min using continuous external fetal monitoring to assess FHR and its relationship to FM (see Gynecology, *First and Second Trimester Bleeding, GY10*)

Normal NST: 2 accelerations, >15 bpm from baseline, lasting >15 s in 20 min

Indication
- any suggestion of uteroplacental insufficiency or suspected fetal compromise

Table 5. Classification of Intrapartum EFM Tracings

	Normal Tracing (Category 1)	Atypical Tracing (Category 2)	Abnormal Tracing (Category 3)
Baseline	110-160 bpm	100-110 bpm or >160 bpm for 30-80 min Rising baseline Arrhythmia	Bradycardia <100 bpm Tachycardia >160 for >80 min Erratic baseline
Variability	6-25 bpm (moderate) ≤5 (absent or minimal) for <40 min	≤5 (absent or minimal) for 40-80 min	≤5 for >80 min ≥25 bpm for >10 min Sinusoidal
Decelerations	None Non-repetitive uncomplicated variable Early decelerations	Repetitive uncomplicated variables Non-repetitive complicated variables Intermittent late decelerations Single prolonged deceleration ≥2 min but <3 min	Repetitive complicated variables Recurrent late decelerations Single prolonged deceleration ≥3 min but <10 min
Acceleration	Spontaneous accelerations but not required Acceleration with scalp stimulation	Absence of acceleration with scalp stimulation	Usually absent (accelerations, if present, do not change classification of tracing)
Interpret Clinically	No evidence of fetal compromise	Physiologic response	Possible fetal compromise

Adapted from: SOGC, Fetal Health Surveillance: Intrapartum Consensus Guideline, March 2020

Describing NSTs: baseline rate, absent/minimal/moderate/marked variability, accelerations present/not present, decelerations early/late/variable

Reassuring BPP (8/8)

LAMB
Limb extension + flexion
AFV 2 cm x 2 cm
Movement (3 discrete)
Breathing (one episode x 30 s)

Operating Characteristics
- false positive rate depends on duration; false negative rate = 0.2-0.3%

Interpretation
- normal, >32 wk GA: at least 2 accelerations of FHR ≥15 bpm from the baseline lasting ≥15 s in 20 min
- normal, <32 wk GA: at least 2 accelerations of FHR ≥10 bpm from the baseline lasting ≥10 s in 20 min
- abnormal: <2 accelerations of FHR in 40 min
- if no observed accelerations or FM in the first 20 min, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 min

BIOPHYSICAL PROFILE

Definition
- U/S assessment of the fetus ± NST

Indications
- postterm pregnancy
- decreased FM
- IUGR
- any other suggestion of fetal distress or uteroplacental insufficiency

Table 6. Ultrasound Scoring Components of the BPP

Parameter	Reassuring (2 points)
Tone	At least one episode of limb extension followed by flexion
Movement	Three discrete movements
Breathing	At least one episode of breathing lasting at least 30 s
Amniotic Fluid Volume (AFV)*	Fluid pocket of 2 cm in 2 axes

*AFV is a marker of chronic hypoxia, all other parameters indicate acute hypoxia

Interpretation
- 8/10 with normal fluid or 10/10: perinatal mortality rate 1:1000; intervention for obstetric and maternal factors
- 6-8/10 with abnormal fluid: perinatal mortality rate 9:1000; determine that there is functioning renal tissue and intact membranes. If so, deliver fetus at term, continue surveillance of preterm fetus <34 wk GA to maximize fetal maturity
- 6/10 with normal fluid: perinatal mortality variable; equivocal test, repeat BPP in 24 h
- 0-4/10: perinatal mortality rate 91-600:1000; consider delivery for fetal indications

Counselling of the Pregnant Patient

Nutrition

- Canada's Food Guide to Healthy Eating suggests
  - eating a varied diet with plenty of vegetables, fruits, whole grains, and protein foods
  - caloric increase of ~100 kCal/d in T1, ~300 kCal/d in T2 and T3, and ~450 kCal/d during lactation (less if BMI >25)
  - daily multivitamin with folic acid should be continued during pregnancy

Nutrients in Pregnancy
- folate: 0.4-1 mg daily in all women starting 2-3 mo preconception until 4-6 wk postpartum; 4 mg if high-risk for NTD starting at least 3 mo preconception until 12 wk GA, then continue 0.4-1 mg until 4-6 wk postpartum or as long as breastfeeding continues
  - supports increase in blood volume, growth of maternal and fetal tissue, and decrease in incidence of NTD
  - foods rich in folic acid include: spinach, lentils, chickpeas, asparagus, broccoli, peas, brussels sprouts, corn, and oranges
- calcium: 1200-1500 mg/d
  - maintains integrity of maternal bones, skeletal development of fetus, and breast milk production
- vitamin D: 1000-2000 IU
  - promotes calcium absorption
- iron: 16-20 mg elemental iron/d
  - supports maternal increase in blood cell mass, supports fetal and placental tissue
  - required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
  - iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see *Iron and Folate Deficiency Anemia, OB28*)
- essential fatty acids – supports fetal neural and visual development
  - contained in vegetable oils, margarines, peanuts, and fatty fish
  - Could also take a 200mg DHA supplement

Caffeine
- diuretic and stimulant that readily crosses placenta
- less than 300 mg/d is considered safe
- relationship between caffeine and IUGR is unknown (ACOG)
- SOGC states 1-2 cups/d of coffee are safe during pregnancy

Sources of Caffeine
- 5 oz cup coffee: 40-180 mg
- 5 oz brewed tea: 20-90 mg
- 12 oz cola: 46 mg
- Red Bull®: 67 mg
- Dark chocolate bar: 10 mg
- 8 oz hot chocolate: 5 mg

Herbal Teas and Preparations
- not enough scientific information about safety of various herbs and herbal products to recommend their use during pregnancy
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- raspberry leaf tea often used at term to promote labour
- herbal teas considered safe in moderation (2-3 cups/d): citrus peel, ginger, lemon balm, linden flower (unless cardiac condition), orange peel, and rose hip

Foodborne Illnesses
- microbiological contamination of food may occur through cross-contamination and/or improper food handling
  - listeriosis (*Listeria monocytogenes*) and toxoplasmosis (*Toxoplasma gondii*) are of concern during pregnancy
  - avoid consumption of raw meats and fish, raw hotdogs, raw eggs, raw sprouts (especially alfalfa), and unpasteurized dairy products or juices
  - avoid unpasteurized soft cheeses, deli meats, smoked salmon, and pâtés as they may be sources of *Listeria*
- chemical contamination of food
  - current guideline for mercury of 0.5 ppm in fish is not considered harmful for the general population, including pregnant women
  - Health Canada advises pregnant women to limit consumption of top predator fish such as shark, swordfish, king mackerel, and tilefish

Lifestyle
- physical activity: 150 min of moderate-intensity per wk; "talk test" = should be able to speak while exercising; avoid supine position after 20 wk GA
- absolute contraindications of physical activity
  - ruptured membranes, PTL, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestations (>3), placenta previa after 28 wk GA, persistent T2 or T3 bleeding, uncontrolled T1DM, uncontrolled thyroid disease, serious cardiovascular or respiratory disease, and other systemic disorders
- relative contraindications of physical activity
  - recurrent pregnancy loss, gestational HTN, history of spontaneous preterm birth, mild/moderate cardiovascular or respiratory disease, symptomatic anemia, malnutrition, eating disorder, twin pregnancy after 28 wk GA, and other significant medical conditions
- weight gain: optimal gain depends on pre-pregnancy BMI (varies from 6.8-18.2 kg)
- work: strenuous work, extended hours, and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
- air travel: acceptable in T2; airline cut off for travel is 36-38 wk GA depending on the airline (may be earlier for long-haul flights), to avoid giving birth on the plane
- sexual intercourse: may continue, except in patients at risk for: spontaneous abortion, PTL, or placenta previa; breast stimulation may induce uterine activity, and is discouraged in high-risk patients near term
- smoking: assist/encourage to reduce or quit smoking (see Family Medicine, FM3)
  - increased risk of decreased birth weight, placenta previa/abruption, spontaneous abortion, PTL, and stillbirth
  - psychosocial interventions considered first-line, nicotine replacement therapy, and/or pharmacotherapy if counselling unsuccessful
  - lowest effective dose to minimize fetal exposure, intermittent dosage preparations preferred
  - limited safety data for bupropion and varenicline use during pregnancy
- alcohol: no amount of alcohol is safe in pregnancy; encourage abstinence from alcohol during pregnancy; alcohol increases incidence of spontaneous abortion, stillbirth, and congenital anomalies
  - fetal alcohol spectrum disorder (see Pediatrics, P29)
- cocaine: microcephaly, growth retardation, prematurity, and placental abruption
- cannabis: associated with low birth weight infants and risk of neurobehavioural abnormalities in childhood
- biopsychosocial considerations: discuss adjustment to pregnancy (e.g. mood, work, stress, family) and birth plan, refer to counselling or community resources as necessary

Weight Gain in Pregnancy

BMI	Total Gain in T2 & T3	Weekly Gain
<18.5	28-40 lb	1-1.3 lb/wk
18.5-24.9	25-35 lb	1 lb/wk
25-29.9	15-25 lb	0.5-0.7 lb/wk
>30	11-20 lb	0.4-0.6 lb/wk

Medications

- most drugs cross the placenta to some extent
- very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
- use any drug with caution and only if necessary
- analgesics: acetaminophen preferable to ASA or ibuprofen

Table 7. Documented Adverse Effects, Weigh Benefits vs. Risks, and Consider Medication Change

Contraindicated Medication	Adverse Effect
ACE Inhibitor	Fetal renal defects, IUGR, oligohydramnios
Carbamazepine	ONTD in 1-2%
Chloramphenicol	Grey baby syndrome (fetal circulatory collapse 2° to toxic accumulation)
Lithium	Ebstein's cardiac anomaly, goitre, hyponatremia
Misoprostol	Mobius syndrome (congenital facial paralysis with or without limb defects), spontaneous abortion, PTL
NSAIDs	Premature closure of the ductus arteriosus after 30 wk GA (prior to that, indomethacin used for tocolysis)
Phenytoin	Fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmorphogenesis, congenital anomalies)
Retinoids (e.g. Accutane®)	CNS, craniofacial, cardiac, and thymic anomalies
Sulpha drugs	Anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3
Tetracycline	Stains infant's teeth, may affect long bone development
Valproate	Congenital malformation (including ONTD) up to 9%
Warfarin	Increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR, fetal warfarin syndrome (nasal hypoplasia, epiphyseal stippling, optic atrophy, mental retardation, intracranial hemorrhage)

Drug Resources During Pregnancy and Breastfeeding
- Hale T. Medications and mothers' milk, 18th ed. Springer Publishing Company, 2019
- Lactmed: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Immunizations

Intrapartum
- administration is dependent on the risk of infection vs. risk of immunization complications
- safe: tetanus toxoid, diphtheria, influenza, hepatitis B, and pertussis
- avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, and varicella
- contraindicated: oral typhoid
- the Public Health Agency of Canada recommends:
  - all pregnant patients receive the influenza vaccine
  - all pregnant patients should be given Tdap every pregnancy irrespective of immunization history. Ideally between 27-32 wk GA but can be given at 13-26 wk GA if high-risk of PTL

Postpartum
- rubella vaccine for all non-immune patients. If they have had an adult booster and remain non-immune, they should not be revaccinated and pregnancy should be deferred for at least 1 mo following vaccination
- hepatitis B vaccine should be given to infants within 12 h of birth if maternal status unknown or positive or if father is known to have chronic hepatitis B infection – follow-up doses at 1 and 6 mo
- any vaccine required/recommended is generally safe postpartum
- delayed postpartum vaccination is recommended if patient receives immunoglobulin or blood products (e.g. RhIg or packed red blood cells)

Radiation

- ionizing radiation exposure is considered teratogenic at high doses
  - if indicated for maternal health, should be done
- imaging not involving direct abdominal/pelvic high dosage radiation is not associated with adverse effects
  - higher dosage of radiation to fetus occurs with plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen/pelvis/lumbar spine
- radioactive isotopes of iodine are contraindicated
- no known adverse effects from U/S or MRI (long-term effects of gadolinium unknown, avoid if possible)

Table 8. Approximate Fetal Doses from Common Diagnostic Procedures

Examination	Estimated Fetal Dose (cGy)	Number of Exams Safe in Pregnancy
Plain Film		
Abdomen	0-14	35
Pelvis	0-11	45
Lumbar spine	0-17	29
Thoracic spine	0.009	555
Chest (2 views)	<0.001	5000
CT		
Abdomen	0-8	6
Pelvis	2-5	2
Lumbar spine	0-24	20
Chest	0.006	833

Adapted from: Cohen-Kerem, et al. 2005 and Valentin 2000

Radiation in Pregnancy

Necessary amount to cause miscarriage: >5 cGy

Necessary amount to cause malformations: >20-30 cGy

Antepartum Hemorrhage

• see Gynecology, *First and Second Trimester Bleeding, GY20*

Definition

• vaginal bleeding from 20 wk GA to term

Differential Diagnosis

• bloody show (represents cervical changes/early stages of dilation) – most common physiologic etiology in T3
• placenta previa
• placental abruption (abruptio placentae) – most common pathological etiology in T3
• vasa previa
• cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
• uterine rupture
• other: bleeding from bowel or bladder, abnormal coagulation

Table 9. Comparison of Placenta Previa and Abruptio Placentae

	Placenta Previa	Placental Abruption
Definition	Abnormal location of the placenta near, partially, or completely over the internal cervical os	Premature separation of a normally implanted placenta after 20 wk GA
Etiology	Idiopathic	Idiopathic
Epidemiology	0.5-0.8% of all pregnancies	1-2% of all pregnancies
Risk Factors	History of placenta previa (4-8% recurrence risk) Multiparity Increased maternal age Multiple gestation Uterine tumour (e.g. fibroids) or other uterine anomalies Uterine scar due to previous abortion, CD, D&C, myomectomy	Previous abruption (recurrence rate 5-16%) Maternal HTN (chronic or gestational HTN in 50% of abruptions) or vascular disease Cigarette smoking (>1 pack/d), excessive alcohol consumption, cocaine Multiparity and/or maternal age >35 yr PPROM Rapid decompression of a distended uterus (polyhydramnios, multiple gestation) Uterine anomaly, fibroids Trauma (e.g. motor vehicle collision, maternal battery)
Bleeding	PAINLESS	Usually PAINFUL

Placenta Previa

Definition

• placenta implanted in the lower segment of the uterus covering the internal cervical os (either fully or partially)
• placental location is described in relation to the internal os as "mm away" or "mm of overlap"

Clinical Features

• PAINLESS bright red vaginal bleeding (recurrent), may be minimal and cease spontaneously but can become catastrophic
• mean onset of bleeding is 30 wk GA, but onset depends on degree of previa
• physical exam
  ▪ do not perform digital vaginal exam until placenta previa ruled out (speculum and transvaginal probe are safe)
  ▪ uterus soft and non-tender
  ▪ presenting fetal part high or displaced
  ▪ FHR usually normal
  ▪ shock/anemia correspond to degree of apparent blood loss

Do NOT perform a vaginal exam until placenta previa has been ruled out by U/S

- complications
  - fetal
    - perinatal mortality low but still higher than with a normal pregnancy
    - prematurity (bleeding often dictates early CD)
    - intrauterine hypoxia (acute or IUGR)
    - fetal malpresentation
    - PPROM
    - risk of fetal blood loss from placenta, especially if incised during CD
  - maternal
    - <1% maternal mortality
    - hemorrhage and hypovolemic shock, anemia, acute renal failure, and pituitary necrosis (Sheehan syndrome)
    - placenta accreta – especially if previous uterine surgery or anterior placenta previa
    - hysterectomy

Investigations
- transvaginal U/S is more accurate than transabdominal U/S at diagnosing placenta previa at any GA
- spontaneously resolution is likely with increasing uterine distention if the placenta covers the internal os by <20 mm at 20 wk GA
- transvaginal U/S should be repeated in T3 as continued change in the placental location is likely

Management
- goal: keep pregnancy intrauterine until the risk of continuing pregnancy outweighs the risk of preterm delivery
- stabilize and monitor
  - maternal stabilization: large bore IV with volume replacement, O_2 for hypotensive patients
  - maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, INR/PTT, fibrinogen, FDP, type, and crossmatch)
  - EFM
  - U/S assessment: when fetal and maternal conditions permit, determine fetal viability, GA, and placental location
- Rhogam® if patient is Rh-negative
- Flow Cytometry and Kleihauer-Betke methods determine extent of fetomaternal transfusion and this helps to administer Rhogam® at adequate dose
- <37 wk GA and minimal bleeding: expectant management
  - admit to hospital
  - limited physical activity
  - pelvic rest (,no douches, enemas, or sexual intercourse)
  - consider corticosteroids for fetal lung maturity
  - delivery when fetus is mature or hemorrhage indicating maternal or fetal compromise
- ≥37 wk GA: deliver by CD

Placental Abruption

Definition
- partial or total placental detachment that is premature and caused by bleeding at the decidual-placental interface
- occurs >20 wk GA (placental detachment <20 wk GA is classified as an abortion)

Placental abruption is the most common cause of DIC in pregnancy

Clinical Features
- classification
  - total (fetal death inevitable) vs. partial
  - external/revealed/apparent: blood dissects downward toward cervix
  - internal/concealed/occult (20%): blood dissects upward toward fetus, may or may not present with vaginal bleeding
    - most are mixed
- presentation
  - usually PAINFUL (80%) vaginal bleeding (bleeding not always present if abruption is concealed), uterine tenderness, uterine contractions/hypertonus (lack of relaxation between contractions)
  - pain: sudden onset, constant, localized to lower back and uterus
  - shock/anemia out of proportion to apparent blood loss
  - ± fetal distress, fetal demise (15% present with demise), bloody amniotic fluid (fetal presentation typically normal)
  - ± coagulopathy

Complications
- fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
- maternal complications: <1% maternal mortality, disseminated intravascular coagulation (DIC) (in 20% of abruptions), acute renal failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), amniotic fluid embolus

Investigations
- clinical diagnosis, U/S not sensitive for diagnosing abruption (sensitivity 15%)

Management
- maternal stabilization: large bore IV with volume replacement, O_2 for hypotensive patients
- maternal monitoring: vitals, urine output, blood loss, blood work (CBC, PTT/PT, fibrinogen, FDP, type, and crossmatch)
- EFM
- blood products available (red cells, platelets, cryoprecipitate) because of DIC risk
- Rhogam® if Rh negative
  - Flow Cytometry and Kleihauer-Betke test to assess dosing of Rhogam®, may confirm abruption (not diagnostic)
- abruption without fetal/maternal compromise (mild abruption)
  - <37 wk GA: use serial hemoglobin to assess concealed bleeding, deliver when fetus is mature or when hemorrhage dictates
  - ≥37 wk GA: stabilize and deliver
- abruption with fetal/maternal compromise (moderate to severe abruption)
  - hydrate and restore blood loss and correct coagulation defect if present
  - vaginal delivery if no contraindication and no evidence of fetal or maternal distress
  - CD if live fetus and fetal or maternal distress develops with fluid/blood replacement, labour fails to progress, or if vaginal delivery otherwise contraindicated

Kleihauer-Betke Test
Quantifies fetal cells in the maternal circulation

Vasa Previa

Definition
- unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord into membranes of placenta or succenturiate (accessory) lobe

Epidemiology
- 1 in 5000 deliveries – higher in twin pregnancies

Clinical Features
- PAINLESS vaginal bleeding and fetal distress (tachy-to-bradyarrhythmia in a sinusoidal pattern)
- if undiagnosed, 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of exsanguination)
- if diagnosed antenatally on U/S without labour or symptoms, then 97% survival

Investigations
- Apt test (NaOH mixed with the blood) can be done immediately to determine if the source of bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
- Wright's stain on blood smear and look for nucleated red blood cells (in cord, not maternal blood)

Management
- planned CD (35-36 wk GA) or if bleeding, emergency CD (since bleeding is from fetus, a small amount of blood loss can have catastrophic consequences)

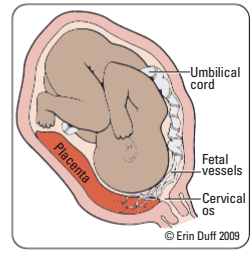


Figure 3. Vasa previa

Obstetrical Complications

Preterm Labour

Definition
- labour between 20 and 37 wk GA

Epidemiology
- PTL complicates approximately 10% of pregnancies

Etiology
- idiopathic
- maternal: infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), HTN, DM, chronic illness, mechanical factors (previous obstetric, gynecological, and abdominal surgeries); socio-environmental (poor nutrition, smoking, drugs, alcohol, stress), preeclampsia, advanced reproductive age
- maternal-fetal: **PPROM**, polyhydramnios, placenta previa, placental abruption, placental insufficiency
- fetal: multiple gestation, congenital abnormalities, fetal hydrops
- uterine: excessive enlargement (hydramnios, multiple gestation), malformations (intracavitary leiomyomas, septate uterus, and Müllerian duct abnormalities)

PTL is the most common cause of neonatal mortality in the United States and is within the top 5 causes of neonatal mortality in Canada

Positive fetal fibronectin in cervicovaginal fluid (>50 ng/mL) at 24 wk GA predicted spontaneous PTL at <34 wk GA with sensitivity 23%, specificity 97%, PPV 25%, NPV 96%

Risk Factors
- prior history of spontaneous PTL is the most important risk factor
- prior history of large or multiple cervical excisions (cone biopsy) or mechanical dilatation (D&C)
- cervical length: measured by transvaginal U/S (cervical length >30 mm has high negative predictive value for PTL before 34 wk GA)
- identification of bacterial vaginosis and *Ureaplasma urealyticum* infections
  - routine screening not supported by current data, but it is reasonable to screen high-risk women
- family history of preterm birth
- smoking
- late maternal age
- multiple gestation
- cocaine

Prevention of Preterm Labour
A. Cervical Cerclage
- definition: placement of cervical sutures at the level of the internal os, usually at the end of T1 or in T2 and removed in T3
- indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
- diagnosis of cervical incompetence
  - obstetrical Hx: silent cervical dilation, recurrent T2 losses, cervical procedures such as loop excisions
  - transvaginal U/S of cervical length is recommended only for high-risk pregnancies and only before 28 wk GA
- proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. conization of the cervix, connective tissue disorders)

B. Progesterone
- progesterone thought to maintain uterine quiescence; however, exact mechanism of action is unclear
- indicated if cervical length is <25 mm at <24 wk GA
- if short cervix: 200 mg vaginally once daily from time of diagnosis to 36 wk GA
- if risk factors or Hx of PTL present, give vaginally starting at 16-20 wk GA
- superior to cerclage in preventing PTL of singletons NOT due to cervical incompetence

C. Lifestyle Modification
- smoking cessation, substance use reduction, treatment of GU infections (including asymptomatic UTIs), and patient education regarding risk factors

Predicting Preterm Labour
- fetal fibronectin: a glycoprotein in amniotic fluid and placental tissue
  - positive if >50 ng/mL; NPV > PPV
  - done if one or more signs of PTL (regular contractions >6/h, pelvic pressure, low abdominal pain and/or cramps, low backache)
  - done only if: 24-34 wk GA, intact membranes, <3 cm dilated, established fetal well-being
  - contraindicated if: cerclage, active vaginal bleeding, vaginal exam, or sex in last 24 h
  - if negative, not likely to deliver in 7-14 d (>95% accuracy); if positive, increased risk of delivery, may need admission/transfer to centre that can do delivery ± tocolysis and/or corticosteroids

Clinical Features
- regular contractions (2 in 10 min, >6/h)
- cervix >1 cm dilated, >80% effaced, or length <2.5 cm

Management
A. Initial
- transfer to appropriate facility if stable
  - tocolysis and first dose of antenatal steroids prior to transfer
- hydration (normal saline at 150 mL/h)
- bed rest in LLDP to reduce aortocaval compression and improve cardiac output
- analgesia (morphine)
- avoid repeated pelvic exams (increased infection risk)
- U/S examination of fetus (GA, BPP, presentation, placenta location, EFW)
- prophylactic antibiotics (for GBS); important to consider if PPROM (e.g. erythromycin controversial, but may help to delay delivery)

B. Tocolysis (Suppression of Labour)
- does not inhibit PTL completely, but may delay delivery (used for <48 h) to allow for betamethasone valerate (Celestone®) and/or transfer to appropriate centre for care of the premature infant
- requirements (all must be satisfied):
  - PTL
  - live, immature fetus, intact membranes, cervical dilatation of <4 cm
  - absence of maternal or fetal contraindications

Ultrasonographic Cervical Length Assessment in Predicting Preterm Birth in Singleton Pregnancies
J Obstet Gynaecol Can 2018;40:154-161
Recommendations:
1. Transabdominal ultrasonography should not be used for cervical length assessment to predict preterm birth (II-2D).
2. Transvaginal ultrasonography is the preferred route for cervical assessment to identify women at increased risk of spontaneous preterm birth and may be offered to women at increased risk of preterm birth (II-2B).
3. Transperineal ultrasonography may be offered to women at increased risk of preterm birth if transvaginal ultrasonography is either unacceptable or unavailable (II-2B).
4. Because of poor positive predictive values and sensitivities and lack of proven effective interventions, routine transvaginal cervical length assessment is not recommended in women at low-risk (II-2E).
5. In women presenting with suspected PTL, transvaginal sonographic assessment of cervical length may be used to help in determining who is at high-risk of preterm delivery and may be helpful in preventing unnecessary intervention. It is unclear whether this information results in a reduced risk of preterm birth (II-2B) .
6. In asymptomatic women with a history of spontaneous preterm birth and an ultrasonographically diagnosed short cervical length (<25 mm) prior to 24 wk GA, cervical cerclage should be considered to reduce the risk of preterm birth (I-B).
7. In all asymptomatic women who present with membranes at or protruding past the external cervical os, an emergency cerclage should be considered to reduce the risk of preterm delivery (I-B).

Physical Examination-Indicated Cerclage: A Systematic Review and Meta-Analysis
Obstet Gynecol 2017;126:125-135
Purpose: To estimate the effectiveness of physical examination-indicated cerclage in the setting of T2 cervical dilatation.
Methods: Meta-analysis of studies identified on MEDLINE, EMBASE, Scopus, ClinicalTrials.gov, Web of Science, and the Cochrane Library.
Results: 10 trials, 757 women (485 underwent cerclage and 272 were expectantly managed). Studies compared cerclage with no cerclage in women with a physical examination that revealed cervical dilatation of ≥0.5 cm between 14 and 27 wk GA. Survival was more likely in the cerclage group (71%) compared to the expectantly managed group (47%) (RR=1.65, 95% CI 1.19-2.28). Cerclage was also associated with a significant prolongation of pregnancy (average 33.98 d, 95% CI 17.88-50.08), greater GA at delivery (mean difference 4.62 wk, 95% CI 3.89-5.36) and significant reductions in preterm birth between 24 and 28 wk GA (8% compared to 37%; RR=0.23, 95% CI 0.13-0.41) and at less than 34 wk GA (50% compared to 82%; RR=0.55, 95% CI 0.38-0.80).
Conclusions: Physical examination-indicated cerclage is associated with significant reductions in perinatal mortality and preterm birth. RCTs are warranted for additional investigation.

- contraindications:
  - maternal: bleeding (placenta previa or abruption), maternal disease (HTN, DM, heart disease), preeclampsia or eclampsia, chorioamnionitis
  - fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)
- agents:
  - calcium channel blockers: nifedipine
    - 20 mg PO loading dose followed by 20 mg PO 90 min later
    - 20 mg can be continued q3-8 h for 72 h or to a maximum of 180 mg
    - 10 mg PO q20 min x 4 doses
    - relative contraindications: nifedipine allergy, hypotension, hepatic dysfunction, concurrent β-mimetics or $MgSO_4$ use, transdermal nitrates, or other antihypertensive medications
    - absolute contraindications: maternal CHF, aortic stenosis
  - prostaglandin synthesis inhibitors: indomethacin
    - first-line for early PTL (<32 wk GA) or polyhydramnios
    - 50-100 mg PR loading dose followed by 25-50 mg q6 h x 8 doses for 48 h
    - contraindications : renal/hepatic impairment, peptic ulcer disease

C. Antenatal Corticosteroids

- betamethasone valerate (Celestone®) 12 mg IM q24 h x 2 doses or dexamethasone 6 mg IM q12 h x 4 doses
  - given between 24 to 34+6 wk GA if expected to deliver in the next 7 d
  - patients between 22+0 and 23+6 wk GA at high-risk of preterm birth within the next 7 d should be provided with multidisciplinary consultation regarding high likelihood for severe perinatal morbidity and mortality and associated maternal morbidity – consider antenatal corticosteroid therapy if early intensive care is requested and planned
  - specific maternal contraindications: active TB
- enhance fetal lung maturity, reduce perinatal death, and reduce incidence of severe RDS, IVH, necrotizing enterocolitis, or neonatal sepsis

D. Neuroprotection

- $MgSO_4$ 4 g bolus followed by 1 g/h infusion for at least 4 h if imminent delivery expected and ≤33+6 wk GA
  - $MgSO_4$ reduces risk of cerebral palsy

Prognosis

- prematurity is the leading cause of perinatal morbidity and mortality
- 24 wk GA = 50% survival (may be higher in tertiary care centres with level 3-4 NICU)
- 30 wk GA or 1500 g (3.3 lb) = 90% survival
- 33 wk GA or 2000 g (4.4 lb) = 99% survival
- morbidity due to asphyxia, hypoxia, sepsis, RDS, IVH, thermal instability, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis

Prelabour Rupture of Membranes

Definitions

- PROM: prelabour rupture of membranes
- prolonged ROM:>18 h elapsed between ROM and onset of labour
- PPROM: preterm (before 37 wk GA) PROM

Risk Factors

- maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STI, UTI), family history of PROM, low socioeconomic class/poor nutrition
- fetal: congenital anomaly, multiple gestation
- other risk factors associated with PTL

Clinical Features

- history of fluid gush or continued leakage

Investigations

- sterile speculum exam (avoid introduction of infection)
  - pooling of fluid in the posterior fornix
  - cascading: fluid leaking out of cervix with cough/valsalva
- nitrazine (basic amniotic fluid turns nitrazine paper blue)
  - low specificity as it can also be positive with blood, urine, or semen
- ferning: salt in amniotic fluid evaporates, giving amniotic fluid the appearance of ferns on microscopy
- U/S to rule out fetal anomalies (if no prior routine anatomy scan); assess EFW, presentation, and BPP

Tocolytics for Preterm Premature Rupture of Membranes
Cochrane DB Syst Rev 2014;2:CD007062
Purpose: To assess the potential benefits and harms of tocolysis in women with PPROM.
Selection Criteria: Pregnant women with singleton pregnancies and PPROM (23-36+6 wk GA).
Results: 8 studies with 408 women total. Prophylactic tocolysis with PPROM was associated with increased overall latency, without additional benefits for maternal/neonatal outcomes. For women with PPROM before 34 wk GA, there was a significantly increased risk of chorioamnionitis in women who received tocolysis. Neonatal outcomes were not significantly different.
Conclusions: Although there are limitations to the studies, there is currently insufficient evidence to support tocolytic therapy for women with PPROM, as there was an increase in maternal chorioamnionitis without significant benefits to the infant.

Prematurity increases newborn risk of:
Respiratory distress
Hypoglycemia
Hyperbilirubinemia
Apnea
Feeding difficulties
Seizures
And more

Membrane status determined by
Pooling of fluid on speculum exam
Increased pH of vaginal fluid (nitrazine test)
Ferning of fluid under light microscopy
Decreased AFV on U/S

Antibiotic Therapy in Preterm Premature Rupture of the Membranes
J Obstet Gynaecol Can 2017;39:207-212
Recommendations:
1. Following PPROM, antibiotics should be administered to women who are not in labour in order to prolong pregnancy and to decrease maternal and neonatal morbidity.
2. The benefit of antibiotics is greater at earlier GAs.
3. Antibiotics of choice are penicillins or macrolide antibiotics (erythromycin) in parenteral and/or oral forms. In patients allergic to penicillin, macrolide antibiotics should be used alone.
4. Two possible regimen options from large PPROM RCTs are: (1) ampicillin 2 g IV q6 h and erythromycin 250 mg IV q6 h for 48 h followed by amoxicillin 250 mg PO q8 h and erythromycin 333 mg PO q8 h for 5 d; (2) erythromycin 250 mg PO q6 h for 10 d.
5. Amoxicillin/clavulanic acid should not be used because of an increased risk of necrotizing enterocolitis in neonates. Amoxicillin without clavulanic acid is safe.
6. Women presenting with PPROM should be screened for UTIs, STIs, and GBS.

Management
- admit for expectant management and monitor vitals (including temperature) q4 h, daily NST, WBC count, surveillance for infection
- avoid introducing infection by minimizing vaginal examinations
  - consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <35 wk GA and no evidence of infection
  - consider tocolysis for 48 h to permit administration of steroids if PPROM induces labour
- screen patients for UTIs, STIs, GBS infection, and treat with appropriate antibiotics if positive (treat GBS at time of labour)
- if not in labour or labour not indicated, start antibiotics to increase latency to labour
- deliver urgently if evidence of fetal distress and/or chorioamnionitis

Table 10. PROM Management

Gestational Age	Management
22-25 wk	Individual consideration with counselling of parents regarding risks to preterm infants
26-34 wk	Expectant management as prematurity complications are significant
34-36 wk	"Grey zone" where risk of death from RDS and neonatal sepsis is the same
≥37 wk	Induction of labour since the risk of death from sepsis is greater than RDS

Prognosis
- varies with GA
- 90% of patients with PROM at 28-34 wk GA go into spontaneous labour within 1 wk
- 50% of patients with PROM at <26 wk GA go into spontaneous labour within 1 wk
- complications: cord prolapse, intrauterine infection (chorioamnionitis), premature delivery, limb contracture, and pulmonary hypoplasia especially if PROM occurs at very early GA

Postterm Pregnancy

Definition
- pregnancy >42 wk GA

Epidemiology
- 41 wk GA: up to 27%
- >42 wk GA: 5.5%

Etiology
- most cases are idiopathic
- increased in anencephalic fetus with no pituitary gland
- placental sulfatase deficiency (X-linked recessive condition, incidence ranges from 1 in 2000 to 1 in 6000 births)
- incorrect dates

Management (for singleton, cephalic fetus, otherwise uncomplicated)
- labour induction is recommended at 41+3 wk GA if no contraindications to vaginal delivery (see *Induction and Augmentation of Labour, OB38*)

Prognosis
- if >42 wk GA, perinatal mortality 2-3x higher (due to progressive uteroplacental insufficiency)
- with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental ageing and infarction, macrosomia, dystocia, fetal distress, operative deliveries, pneumonia, seizures, NICU admission, stillbirth
- morbidity increased with gestational HTN, DM, placental abruption, IUGR, advanced reproductive age, and multiple gestation

Intrauterine Fetal Demise

Definition
- fetal demise *in utero* after 20 wk GA (before 20 wk GA is called spontaneous abortion)

Epidemiology
- occurring in <1% of pregnancies (in 2021, there were 3,174 stillbirths in Canada) – increased in high-risk pregnancies

Etiology
- 50% idiopathic
- 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, and APS

Clinical Features
- decreased perception of FM by patient
- SFH and maternal weight not increasing
- absent fetal heart tones on Doppler (not diagnostic)
- high MSAFP
- on U/S: no FHR. Depending on timing of death, may see skull collapse, brain tissue retraction, empty fetal bladder, non-filled aorta, or poor visualization of midline falx

Management
- diagnosis: absent cardiac activity and FM on U/S (required)
- determine secondary cause
  - maternal: HbA1c, fasting glucose, TSH, Kleihauer-Betke, VDRL, ANA, CBC, anticardiolipins, antibody screens, INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, and TORCH screen
  - fetal: karyotype, cord blood, skin biopsy, genetics evaluation, autopsy, amniotic fluid culture for CMV, parvovirus B19, and herpes
  - placenta: pathology, bacterial cultures

Treatment
- >20 wk GA: IOL with vaginal misoprostol (Cytotec®)
- monitor for maternal coagulopathy (10% risk of DIC)
- parental psychological care/bereavement support as per hospital protocol
- comprehensive discussion within 3 mo about final investigation and post-mortem results, help make plans for future pregnancies

DIC: Generalized Coagulation and Fibrinolysis Leading to Depletion of Coagulation Factors

Obstetrical Causes
- Placental abruption
- Gestational HTN
- Fetal demise
- PPH

DIC-specific Blood Work
- CBC (platelets)
- aPTT and PT (prothrombin time)
- FDP
- Fibrinogen

Treatment
- Treat underlying cause
- Supportive
- Fluids
- Blood products
- FFP, platelets, cryoprecipitate
- Consider anticoagulation as VTE prophylaxis

Intrauterine Growth Restriction

Definition
- failure of a fetus to reach its biologically determined growth potential due to pathological factors

Etiology/Risk Factors
- 50% unknown
- maternal:
  - malnutrition, smoking, drug misuse, alcoholism, cyanotic heart disease, T1DM, SLE, pulmonary insufficiency, previous IUGR (25% risk), chronic HTN, gestational HTN, chronic renal insufficiency, prolonged gestation
- placental:
  - any disease that causes placental insufficiency
  - gross placental morphological abnormalities (infarction, hemangiomas, placenta previa, and abnormal cord insertion)
- fetal:
  - TORCH infections, multiple gestation, and congenital anomalies/chromosomal abnormalities (10%)

Clinical Features
- symmetric/type I (25-30%): occurs early in pregnancy
  - reduced growth of both head and abdomen
  - HC/AC ratio may be normal (>1 up to 32 wk GA; =1 at 32-34 wk GA; <1 after 34 wk GA)
  - usually associated with congenital anomalies or TORCH infections
- asymmetric/type II (70%): occurs late in pregnancy
  - fetal abdomen is disproportionately smaller than fetal head
  - brain is spared; therefore HC/AC ratio increased
  - usually associated with placental insufficiency
  - more favourable prognosis than type I

TORCH
Toxoplasmosis
Others: e.g. syphilis, parvovirus
Rubella
CMV
HSV
See *Table 15, OB31*

- complications
  - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, hypocalcemia, hypophosphatemia, hyponatremia, and intellectual disability
  - greater risk of perinatal morbidity and mortality

Investigations
- SFH measurements at every antepartum visit (ensure accurate GA)
- if mother at high-risk or SFH lags >2 cm behind GA
  - U/S for biparietal diameter, HC/AC ratio, FL, fetal weight, AFV (decrease associated with IUGR), and decrease in the rate of growth
  - ± BPP
  - Doppler analysis of umbilical cord blood flow

Management
- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition, and treat maternal illness
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if >34 wk GA
- optimize fetus with betamethasone valerate (Celestone®), $MgSO_4$ for neuroprotection, early GBS swab, and pediatrics consult if anticipated preterm delivery
- as IUGR fetuses are less likely to withstand stresses of labour, and more likely to be delivered by CD

Macrosomia

Definition
- infant weight ≥90th percentile for a particular GA or >4000 g

Etiology/Risk Factors
- maternal obesity, gestational and pre-gestational DM, past history of macrosomic infant, prolonged gestation, multiparity, excessive maternal weight gain during pregnancy

Clinical Features
- increased risk of perinatal mortality
- CPD and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labour (see *Table 14, OB30*)

Investigations
- serial SFH
- U/S for EFW if mother at high-risk or SFH >2 cm ahead of GA

Management
- prevent hyperglycemia in patients with DM, optimize pre-pregnancy weight, and limit excessive pregnancy weight gain in patients with increased BMI
- planned CD is a reasonable option where EFW >5000 g in non-diabetic patients and EFW >4500 g in diabetic patients

Polyhydramnios/Oligohydramnios

Table 11. Polyhydramnios and Oligohydramnios

	Polyhydramnios	Oligohydramnios
Definition	AFI >25 cm U/S: single deepest pocket >8 cm	AFI <5 cm U/S: single deepest pocket ≤2 cm
Etiology	Idiopathic most common Maternal T1DM: abnormalities of transchorionic flow Maternal-fetal Chorioangiomas Multiple gestation Fetal hydrops (increased erythroblastosis) Fetal Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios) Respiratory: cystic adenomatoid malformed lung CNS: anencephaly, hydrocephalus, meningocele GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfere with swallowing)	Idiopathic most common Maternal Uteroplacental insufficiency (preeclampsia, nephropathy) Medications (ACEI) Fetal Congenital urinary tract anomalies (renal agenesis, obstruction, posterior urethral valves) Demise/chronic hypoxemia (blood shunt away from kidneys to perfuse brain) IUGR Ruptured membranes: prolonged amniotic fluid leak Amniotic fluid normally decreases after 35 wk GA
Epidemiology	Occurs in 0.2-1.6% of all pregnancies	Occurs in ~4.5% of all pregnancies Severe form in <0.7% Common in pregnancies >41 wk GA (~12%)
Clinical Features and Complications	Uterus large for GA, difficulty palpating fetal parts and hearing FHR Maternal complications Pressure symptoms from overdistended uterus (dyspnea, edema, hydronephrosis) Obstetrical complications Cord prolapse, placental abruption, malpresentation, PTL, uterine dysfunction, and PPH	Uterus small for dates Fetal complications 15-25% have fetal anomalies Amniotic fluid bands (T1) can lead to Potter's facies, limb deformities, abdominal wall defects Obstetrical complications Cord compression Increased risk of adverse fetal outcomes Pulmonary hypoplasia (late-onset) Marker for infants who may not tolerate labour well
Management	Determine underlying cause Screen for maternal disease/infection Complete fetal U/S evaluation Depends on severity Mild to moderate cases require no treatment If severe, hospitalize and consider therapeutic amniocentesis	Always warrants admission and investigation Rule out ROM Fetal monitoring (NST, BPP) U/S Doppler studies (umbilical cord and uterine artery) Maternal hydration with oral or IV fluids to help increase amniotic fluid Injection of fluid via amniocentesis will improve condition for ~1 wk – may be most helpful for visualizing any associated fetal anomalies Consider delivery if term Amnio-infusion may be considered during labour via intrauterine catheter
Prognosis	2- to 5-fold increase in risk of perinatal mortality	Poorer with early onset High mortality related to congenital malformations and pulmonary hypoplasia when diagnosed during T2

Antenatal Depression

Definition
- major depression occurring in a patient who is pregnant, onset may be prior to pregnancy

Epidemiology
- occurs in 7-9% of pregnancies

Risk Factors
- prior history of depression, anxiety, unintended or unwanted pregnancy, life stress, intimate partner violence or history of abuse, poor social support, chronic general medical conditions (specifically hypothyroidism)

Clinical Features
- comparable to symptoms of non-pregnant major depressive disorder (see Psychiatry, PS10)
- suspect if: prior history of depression, excessive anxiety about the fetus, poor self-esteem, despondency, anhedonia, non-adherence to antenatal care, poor weight gain due to decreased appetite or inadequate diet, suicidal ideation

Screening
- most widely used is the 10-item Edinburgh Postnatal Depression Scale
- other options include self-administered nine-item Patient Health Questionnaire and 20-item Center for Epidemiologic Studies Depression Scale

Treatment
- structured psychotherapy as first-line treatment for mild to moderate cases with no prior history of major depression
- antidepressants, psychotherapy, supportive care, and electroconvulsive therapy if refractory or if features of psychosis, catatonia, high risk of suicide, and fluid or food refusal leading to dehydration and malnutrition

Prognosis
- may be associated with altered fetal physiologic effects, adverse pregnancy and neonatal outcomes, abnormal infant and child development, or cognitive impairment and psychopathology in the offspring, leading to lasting long-term effects
- increased risk of recurrence after pregnancy, and conversion of the diagnosis to bipolar disorder

Multi-Fetal Gestation and Fetal Malpresentation

Definitions
- multi-fetal gestation: two or more embryos/fetuses occupying the uterus simultaneously
- fetal malpresentation: when fetus is not head-down as birth approaches

Epidemiology
- incidence of twins is 1 in 80 and triplets is 1 in 6400 in North America
- 2/3 of twins are dizygotic (fraternal)
  - risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, and ethnicity (e.g. certain African regions)
- monozygous twinning occurs at a constant rate worldwide (1 in 250)
- determine zygosity by number of placentas, thickness of membranes, sex, and blood type

The Ps of Multiple Gestation Complications

Increased rates of:
Puking
Pallor (anemia)
Preeclampsia/pregnancy-induced HTN
Pressure (compressive symptoms)
PTL/**P**ROM/**PP**ROM
Polyhydramnios
Placenta previa/abruption
PPH/antepartum hemorrhage
Prolonged labour
Cord **P**rolapse
Prematurity
Malpresentation
Perinatal morbidity and mortality
Parental distress
Postpartum depression

Clinical Features

Table 12. Complications Associated with Multiple Gestation

Maternal	Uteroplacental	Fetal
Hyperemesis gravidarum	Increased PROM/PTL	Prematurity
GDM	Polyhydramnios	IUGR
Gestational HTN	Placenta previa	Malpresentation
Anemia	Placental abruption	Congenital anomalies
Increased physiological stress on all systems	PPH (uterine atony)	Twin-twin transfusion syndrome
Increased compressive symptoms	Umbilical cord prolapse	Increased perinatal morbidity and mortality
CD	Cord anomalies	Twin interlocking in MCMA twins (twin A
Thrombosis	(velamentous insertion, 2 vessel cord)	breech, twin B vertex)
		Single fetal demise

Management
- U/S determination of chorionicity must be done within T1 (ideally 8-12 wk GA)
- increased antenatal surveillance
  - serial U/S q2-3 wk from 16 wk GA (monochorionic), q3-4 wk from 18-22 wk GA (uncomplicated diamniotic dichorionic) to assess growth
  - Doppler flow studies weekly if discordant fetal growth (>30%)
  - BPP
- may attempt vaginal delivery (if dichorionic diamniotic or monochorionic diamniotic) if twin A presents as vertex and growth discrepancy <25%, otherwise CD (40-50% of all twin deliveries, 10% of cases have twin A delivered vaginally and twin B delivered by CD)
- all monochorionic monoamniotic twins need to be delivered by CD
- mode of delivery depends on fetal weights, GA, chorionicity, presentation of presenting twin, and patient preference

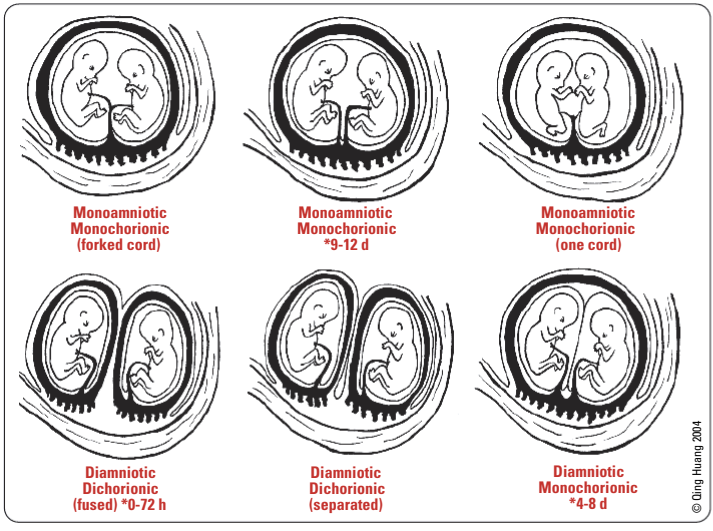


Figure 4. Classification of twin pregnancies
*Indicates time of cleavage

Twin-Twin Transfusion Syndrome

Definition
- formation of placental intertwin vascular anastomoses that can cause arterial blood from donor twin to pass into veins of the recipient twin

Epidemiology
- 10% of monochorionic twins
- concern if >30% discordance in EFW

Clinical Features
- donor twin: IUGR, hypovolemia, hypotension, anemia, and oligohydramnios
- recipient twin: hypervolemia, HTN, CHF, polycythemia, edema, polyhydramnios, and kernicterus in neonatal period

Investigations
- detected by U/S screening, Doppler flow analysis

Management
- fetoscopic laser ablation of placental vascular anastomoses (preferred between 16-26 wk GA)
- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary

Breech Presentation

Definition
- fetal buttocks or lower extremity is the presenting part as determined on U/S
- complete (10%): hips and knees both flexed
- frank (60%): hips flexed, knees extended, buttocks present at cervix
  - most common type of breech presentation
  - most common breech presentation to be delivered vaginally
- incomplete (30%): both or one hip partially flexed and both or one knee present below the buttocks, feet or knees present first (footling breech, kneeling breech)

Epidemiology
- occurs in 3-4% of pregnancies at term (25% at <28 wk GA)

Criteria for Vaginal Breech Delivery

Frank or complete breech, >36 wk GA

EFW 2500-3800 g based on clinical and U/S assessment (5.5–8.5 lb)

Fetal head flexed

Continuous fetal monitoring

Two experienced obstetricians, assistant, and anesthetist present

Ability to perform emergency CD within 30 min if required

Mother motivated for vaginal breech delivery and understands risks and benefits

Risk Factors
- maternal: pelvis (contracted), uterus (shape abnormalities, fibroids, previous breech), pelvic tumours causing compression, and grand multiparity
- placental: placenta previa
- fetal: prematurity, amniotic fluid (poly-/oligohydramnios), multiple gestation, congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations), abnormalities in fetal tone and movement, aneuploidy, hydrocephalus, and anencephaly

Management
- pre- or early-labour U/S to assess type of breech presentation, fetal growth, estimated weight, placenta position, attitude of fetal head (flexed is preferable); if U/S unavailable, recommend CD
- ECV and elective CD should be presented as options with the risks and benefits outlined; obtain informed consent
- **ECV**: procedure that is performed with external pressure on the uterus to encourage a non-vertex fetus (breech, transverse, or oblique) to turn into vertex presentation
  - overall success rate of ~40-60%
  - criteria: >36 wk GA, singleton, unengaged presenting part, reactive NST, intact membranes
  - contraindications:
    - absolute: where vaginal delivery is contraindicated (placenta previa, previous classical CD, previous myomectomy), PROM, uteroplacental insufficiency, abnormal NST, multiple gestation
    - relative: mild/moderate oligohydramnios, suspected IUGR, HTN, previous T3 bleed, nuchal cord
  - risks: abruption, cord compression, cord accident, ROM, labour, fetal bradycardia requiring CD (<1% risk), alloimmunization, fetal death (1/5000)
  - method: tocometry, followed by U/S guided transabdominal manipulation of fetus with intermittent FHR assessment
  - if patient Rh negative, give Rhogam® after the procedure
  - better prognosis if multiparous, good fluid volume, small baby, skilled obstetrician, and posterior placenta
  - if unsuccessful, planned CD or planned vaginal birth
- **vaginal breech delivery**: can be spontaneous or assisted
  - method:
    - encourage effective maternal pushing efforts
    - at delivery of aftercoming head, assistant must apply suprapubic pressure to flex and engage fetal head
    - delivery can be spontaneous or assisted; avoid fetal traction
    - apply fetal manipulation only after spontaneous delivery to level of umbilicus
  - contraindications: cord presentation, footling breech, fetal factors incompatible with vaginal delivery (e.g. hydrocephalus, macrosomia, IUGR), clinically inadequate maternal pelvis
  - risks: head entrapment, prolapsed umbilical cord, birth trauma, perinatal death
- CD recommended if: the breech has not descended to the perineum in the second stage of labour after 2 h, in the absence of active pushing, or if vaginal delivery is not imminent after 1 h of active pushing

Prognosis
- regardless of route of delivery, breech infants have lower birth weights and higher rates of perinatal mortality, congenital anomalies, abruption, and cord prolapse

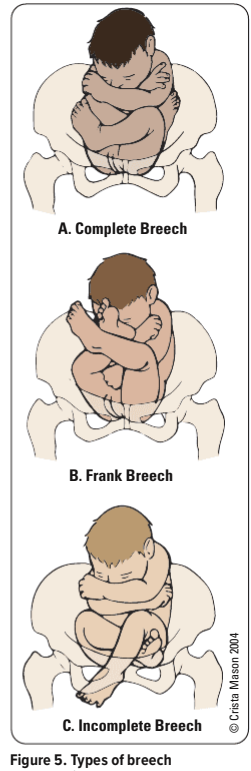


Figure 5. Types of breech presentation

Hypertensive Disorders of Pregnancy

Hypertension in Pregnancy

- hypertensive disorders of pregnancy are classified as either pre-existing or *de novo* (gestational HTN or preeclampsia) and exist on a spectrum

Ominous Symptoms of HTN in Pregnancy
Right upper quadrant pain
Headache
Visual disturbances

PRE-EXISTING HYPERTENSION

Definition
- sBP ≥140 mmHg or dBP ≥90 mmHg prior to 20 wk GA; BP should be elevated on ≥2 occasions at least 15 min apart on the same arm, seated with appropriate sized cuff
- essential HTN is associated with an increased risk of gestational HTN, placental abruption, IUGR, IUFD, and CD
- if HTN persists >12 wk postpartum, the diagnosis is "revised" to pre-existing HTN that was masked by the early pregnancy physiologic decrease in BP

GESTATIONAL HYPERTENSION

Definition
- sBP ≥140 mmHg or dBP ≥90 mmHg after 20 wk GA without proteinuria in a patient known to be normotensive before pregnancy

PREECLAMPSIA

Definition
- pre-existing or gestational HTN with new onset proteinuria (urinary protein:creatinine ratio >30 mg/mmol) or adverse conditions (end organ dysfunction, see *Hypertension in Pregnancy CBM, OB27*)

Eclampsia prior to 20 wk GA is rare and should raise the possibility of an underlying molar pregnancy or APS

ECLAMPSIA

Definition
- the occurrence of ≥1 generalized convulsion and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions

Etiology
- placental malperfusion → soluble factors released into circulation → maternal vascular endothelial injury → hypertension + multi-organ injury

Epidemiology of Eclampsia
- an eclamptic seizure occurs in approximately 0.5% of mildly preeclamptic patients and 2-3% of severely preeclamptic patients

Clinical Manifestation of Eclampsia
- eclampsia is a clinical diagnosis
- typically tonic-clonic and lasting 60-75 s
- symptoms that may occur before the seizure include persistent frontal or occipital headache, blurred vision, photophobia, right upper quadrant or epigastric pain, and altered mental status
- atypical eclampsia can present with no proteinuria or hypertension prior to the seizure
- approximately 25% of cases will present in the postpartum period
- in general, women with typical eclamptic seizures who do not have focal neurologic deficits or prolonged coma do not require diagnostic evaluation, including imaging

Hypertension in Pregnancy

Adverse Maternal Conditions
- sBP >160 mmHg
- dBP >100 mmHg
- HELLP
- Cerebral hemorrhage
- Renal dysfunction: oliguria <500 mL/d
- Left ventricular failure, pulmonary edema
- Placental abruption, DIC
- Abdominal pain, N/V
- Headaches, visual problems
- SOB, chest pain
- Eclampsia: convulsions

Adverse Fetal Conditions
- IUGR
- Oligohydramnios
- Absent/reversed umbilical artery end diastolic flow
- Can result in fetal disability and/or death

Risk Factors for Hypertensive Disorders in Pregnancy
- maternal factors:
  - primigravida (80-90% of gestational HTN), first conception with a new partner, PMHx or FMHx of gestational HTN, or preeclampsia/eclampsia
  - DM, chronic HTN, or renal insufficiency
  - obesity
  - APS or inherited thrombophilia
  - extremes of maternal age (<18 or >40 yr)
  - previous stillbirth or IUFD
  - vascular or connective tissue disease
- fetal factors:
  - IUGR or oligohydramnios
  - GTN
  - multiple gestation
  - fetal hydrops "mirror syndrome"
  - placental abruption in previous pregnancy

Evidence-Recommendation Highlights of SOGC Clinical Practice Guidelines
Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy
J Obstet Gynaecol Can 2022;44:517-571
- Low-risk normotensive women should not be screened for proteinuria
- Home automated BP monitoring should be used to mitigate white-coat syndrome
- Calcium supplementation (of at least 500 mg/d PO) is recommended for women with low dietary intake of calcium (<900 mg/d)
- For preeclampsia prevention among increased risk women, low-dose ASA (81 or 162 mg/d) is recommended from before 16 wk GA until 36 wk GA
- Exercise is recommended to prevent preeclampsia
- Antihypertensive therapy is recommended for all pregnant women with sBP ≥140 mmHg or dBP ≥90 mmHg
- Initial antihypertensive therapy for severe HTN (sBP ≥160 mmHg or dBP ≥110 mmHg) should be with labetalol, nifedipine, methyldopa, or hydralazine
- Initial antihypertensive therapy for non-severe HTN (BP 140-159/90-109 mmHg) should be with labetalol, nifedipine, or methyldopa
- Antenatal corticosteroids for fetal lung maturation should be considered for all women with preeclampsia before 34 wk GA In women with preeclampsia, initiation of delivery is recommended at 37 wk GA
- $MgSO_4$ is the recommended first-line treatment for eclampsia and eclampsia prophylaxis in the case of severe preeclampsia

Clinical Evaluation of Hypertensive Disorders in Pregnancy
- in general, clinical evaluation should include the mother and fetus
- evaluation of mother:
  - body weight
  - central nervous system
    - presence and severity of headache
    - visual disturbances (blurring, scotomata)
    - tremulousness, irritability, and somnolence
    - hyperreflexia
  - hematologic (bleeding, petechiae)
  - hepatic (right upper quadrant or epigastric pain, severe N/V)
  - renal (urine output, colour)
- evaluation of fetus:
  - FM
  - FHR tracing – NST
  - U/S for BPP and EFW
  - Doppler flow studies

Laboratory Evaluation of Hypertensive Disorders in Pregnancy
- CBC – evaluate for thrombocytopenia
- PTT, INR, fibrinogen – if abnormal LFTs or bleeding
- ALT, AST
- creatinine, uric acid
- 24 h urine collection for protein or protein:creatinine ratio
- may consider placental growth factor (PlGF) testing or sFlt-1:PlGF ratio as an early screening test for suspected preeclampsia

Complications of Hypertensive Disorders in Pregnancy
- maternal
  - liver and renal dysfunction
  - seizure - "eclampsia"
  - abruptio placentae
  - left ventricular failure/pulmonary edema
  - DIC (release of placental thromboplastin consumptive coagulopathy)
  - HELLP syndrome
  - hemorrhagic stroke (50% of deaths)
- fetal (secondary to placental insufficiency)
  - IUGR, prematurity, abruptio placentae, IUFD

HELLP Syndrome
Hemolysis
Elevated
Liver Enzymes
Low
Platelets

Management of Hypertension
- for non-severe HTN (BP 149-159/90-109 mmHg): target a BP of <140/90 mmHg in patient without comorbidities, or <140/85 mmHg in patient with comorbidities
  - antihypertensive therapy for both pre-existing and gestational HTN: labetalol 100-400 mg PO BID-TID, nifedipine XL preparation 20-60 mg PO once daily or BID, or α-methyldopa 250-500 mg PO BID-TID
- for severe HTN (BP>160/110 mmHg): target sBP <160 mmHg and dBP <110 mmHg, give one of:
  - labetalol 20 mg IV, then 20-80 mg IV q30 min (max 300 mg), then switch to oral
  - nifedipine immediate release 5-10 mg capsule q30 min
  - hydralazine 5 mg IV, repeat 5-10 mg IV q30 min or 0.5-10 mg/h IV, to a maximum of 20 mg IV (or 30 mg IM)
- no ACEI, ARBs, diuretics (may be used in cases of pulmonary edema or cardiac failure), prazosin, or atenolol
- pre-existing HTN and gestational HTN without any deterioration can be followed until 37 wk GA, then decide to induce shortly thereafter

Management of Preeclampsia
- if stable and no adverse conditions (24-33+6 wk GA): expectant management ± delivery as approaching 34-36 wk GA (must weigh risks of fetal prematurity vs. risks of developing severe preeclampsia/eclampsia)
  - antenatal corticosteroids should be considered if ≤ 35 wk GA
- if >37 wk GA, delivery is recommended
- for severe preeclampsia, stabilize and deliver, regardless of GA
- if severe preeclampsia during labour, increase maternal monitoring: hourly input and output, hourly neurological vitals, and continuous FHR monitoring
- antihypertensive therapy (regimen as above for severe HTN)
- seizure prevention:
  - $MgSO_4$: 4 g IV loading dose, followed by 1g/h
  - postpartum management
  - risk of seizure highest in first 24 h postpartum – continue $MgSO_4$ for 12-24 h after delivery
  - vitals q1 h
  - consider HELLP syndrome
  - most return to a normotensive BP within 2 wk

Management of Eclampsia
- ABCs
- roll patient into LLDP to prevent aspiration
- supplemental O_2 via face mask to treat hypoxemia due to hypoventilation during convulsive episode
- aggressive antihypertensive therapy for sustained sBP ≥160 mmHg or dBP ≥110 mmHg with hydralazine or labetalol
- prevention of recurrent convulsions: to prevent the possible complications of repeated seizure activity (e.g. rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, etc.)
- $MgSO_4$ is the first-line therapy for eclampsia (used for treatment and prophylaxis)
- the definitive treatment of eclampsia is DELIVERY after maternal stabilization, irrespective of GA or fetal distress, to reduce the risk of maternal morbidity and mortality from complications of the disease
  - mode of delivery is dependent on the clinical situation and fetal-maternal condition

Differential Diagnosis of Cause for Seizure in a Pregnant Patient
- Stroke
- Hypertensive disease (hypertensive encephalopathy, pheochromocytoma)
- Space-occupying lesion of the CNS
- Metabolic disorders (hypoglycemia, SIADH)
- Infection (meningitis, encephalitis)
- TTP or thrombophilia
- Idiopathic epilepsy
- Use of illicit drugs
- Cerebral vasculitis

Medical Complications of Pregnancy

Iron and Folate Deficiency Anemia

Table 13. Iron Deficiency and Folate Deficiency Anemia

	Iron Deficiency Anemia	Folate Deficiency Anemia
Etiology	See Hematology, H6	See Hematology, H6
Epidemiology	Responsible for 80% of non-physiologic anemia during pregnancy	Incidence varies from 0.5-25% depending on region, population, and diet
Clinical Features	See Hematology, H6	See Hematology, H6
Investigations	See Hematology, H6	See Hematology, H6
Management	Prevention (non-anemic): 30 mg elemental iron daily (met by most prenatal vitamins) Treatment (anemic): 30-120 mg elemental iron daily 325 mg ferrous fumarate = 106 mg elemental Fe; 325 mg ferrous sulfate = 65 mg elemental Fe; 325 mg ferrous gluconate = 36 mg elemental Fe Polysaccharide-Iron Complex = 150 mg elemental Fe/capsule	Prevention: 0.4-1 mg folic acid PO daily for 1-3 mo preconceptually and throughout T1
Complications	Maternal: angina, CHF, infection, slower recuperation, and PTL Fetal: decreased oxygen carrying capacity leading to fetal distress, IUGR, low birth weight, and fetal neurodevelopment	Maternal: decreased blood volume, N/V, and anorexia Fetal: neural tube defects in T1, low birth weight, and prematurity
Notes	Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg), and losses (200 mg) – more needed for multiple gestations	Minimum daily requirement is 0.4 mg Most often associated with iron deficiency anemia Folic acid is necessary for closure of neural tube during early fetal development (by 28 d GA)

Diabetes Mellitus

Epidemiology
- 2-6% of pregnancies are complicated by DM

Classification of Diabetes Mellitus
- T1DM and T2DM (see Endocrinology, E7)
- GDM: onset of DM during pregnancy (usually tested for around 24-28 wk GA)

Etiology
- pre-existing T1DM and T2DM
- GDM: anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → leading to GDM and/or exacerbating pre-existing DM

Management

A. T1DM and T2DM

Preconception
- pre-plan and refer to high-risk clinic for interprofessional care
- commence folic acid (1.0 mg daily) 3 mo prior to conception
- optimize glycemic control (HbA1c <7%), counsel and assess for risks and complications (retinopathy, neuropathy, CKD, CVD), review medications (discontinue ACEI, ARBs, statins)

Pregnancy
- for T2DM, switch to insulin therapy and discontinue non-insulin antihyperglycemic agents
  - continuing glyburide or metformin is controversial
  - teratogenicity unknown for other oral antihyperglycemics
- tight glycemic control
  - insulin dosage may need to be adjusted as pregnancy advances due to increased demand and increased insulin resistance
- monitor as for normal pregnancy, plus initial 24 h urine protein and creatinine clearance, retinal exam, and HbA1c (aim for <6.5% during pregnancy)
- increased fetal surveillance (fetal growth, BPP, NST) starting in late T2 and T3 and perform weekly after 36 wk GA
- fetal echocardiogram in T2 (if high HbA1c in T1 or just prior to pregnancy) to look for cardiac abnormalities
- start 162 mg ASA at night before 16 wk GA to reduce risk of preeclampsia

Monitoring Glucose Levels
- Frequent measurements of blood glucose during pregnancy are advised for patients with T1DM or T2DM to help prevent or treat both hypoglycemia and hyperglycemia, and also improve neonatal outcomes
- Aim for:
  - FPG ≤5.3 mmol/L (95 mg/dL)
  - 1 h postprandial PG ≤7.8 mmol/L (140 mg/dL)
  - 2 h postprandial PG ≤6.7 mmol/L (120 mg/dL)
  - Most women can be followed with monthly HbA1c determinations

Fasting plasma glucose values seem to be the most effective at determining the likelihood of macrosomia or other adverse pregnancy outcomes

Labour
- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose)
- induce by 38-39 wk GA for uncomplicated pre-existing diabetes, induce earlier if indicated (poor glycemic control, end-organ involvement)
- increased risk of CPD and shoulder dystocia with babies >4000 g, consider elective CD for predicted birth weight >4500 g (controversial)
- monitoring:
  - during labour, monitor blood glucose q1 h with patient on insulin and dextrose drip
  - aim for blood glucose between 4.0-7.0 mmol/L to reduce the risk of neonatal hypoglycemia

Postpartum
- insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
- monitor glucose q6 h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >8 mmol/L

B. GESTATIONAL DM

Screening and Diagnosis
- all pregnant women between 24-28 wk GA
- 2 screening options
  - preferred 2-step screening (recommended by the Canadian Diabetes Association)
    - step 1: perform a random non-fasting 50 g OGCT
      - 1 h PG <7.8 mmol/L is normal
      - 1 h PG ≥11.1 mmol/L is GDM
      - if 1 h PG 7.8-11.0 mmol/L, proceed to Step 2
    - step 2: perform a fasting 75 g OGTT, GDM if ≥1 of:
      - FPG ≥5.3 mmol/L
      - 1 h PG ≥10.6 mmol/L
      - 2 h PG ≥9.0 mmol/L
  - alternative 1-step screening with fasting 75 g OGTT; GDM if ≥1 of:
    - FPG ≥5.1 mmol/L
    - 1 h PG ≥10.0 mmol/L
    - 2 h PG ≥8.5 mmol/L

Risk Factors for GDM
- Age >35 yr
- Obesity (BMI ≥30 kg/m²)
- Increased risk in Indigenous, Hispanic, Asian, and African populations
- FHx of DM
- Previous history of GDM
- Previous child with birthweight >4.0 kg
- Polycystic ovarian syndrome
- Current use of glucocorticoids
- Essential HTN or pregnancy-related HTN

Management
- first-line: diet modification and increased physical activity
- initiate insulin therapy if glycemic targets not achieved within 2 wk of lifestyle modification alone
  - glycemic targets: FPG <5.3 mmol/L, 1 h PG <7.8 mmol/L, 2 h PG <6.7 mmol/L
- metformin can be used in pregnancy but is off-label and should be discussed with patient
- serial BPP/growth starting at 28 wk GA q3-4 wk
- starting at 36 wk, weekly assessment of fetal well-being with either BPP or NST until delivery
- stop insulin and diabetic diet postpartum
- follow up with 75 g OGTT between 6 wk-6 mo postpartum, counsel about lifestyle modifications

Metformin and glyburide are safe during breastfeeding. Other anti-insulin antihyperglycemic agents should not be used due to lack of safety data

Labour
- offer IOL between 38-39 wk GA for GDM on insulin or metformin
- intrapartum glucose management and maternal glucose maintenance between 4.0-7.0 mmol/L

Postpartum
- encourage breastfeeding for 3-4 mo postpartum to prevent childhood obesity and diabetes
- repeat testing for women with previous pregnancy affected by GDM before planning another pregnancy or every 1-3 yr

Prognosis
- most maternal and fetal complications are related to hyperglycemia and its effects
- long-term maternal complications
  - T1DM and T2DM: risk of progressive retinopathy and nephropathy
  - GDM: 50% risk of developing T2DM in next 20 yr

Table 14. Complications of DM in Pregnancy

Maternal	Fetal
Obstetric HTN/preeclampsia (especially if pre-existing nephropathy/proteinuria): insulin resistance is implicated in etiology of HTN Polyhydramnios: maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal polyuria (a major source of amniotic fluid)	**Growth Abnormalities** Macrosomia: maternal hyperglycemia leads to fetal hyperinsulinism resulting in accelerated anabolism IUGR: due to placental vascular insufficiency
Diabetic Emergencies Hypoglycemia Ketoacidosis Diabetic coma	**Delayed Organ Maturity** Fetal lung immaturity: hyperglycemia interferes with surfactant synthesis (RDS)
End-Organ Involvement or Deterioration (occur in T1DM and T2DM, not in GDM) Retinopathy Nephropathy	**Congenital Anomalies (occur in T1DM and T2DM, not in GDM)** 2-7x increased risk of cardiac (ventricular septal defect), NTD, GU (cystic kidneys), GI (anal atresia), and MSK (sacral agenesis) anomalies due to hyperglycemia Note: Pregnancies complicated by GDM do not manifest an increased risk of congenital anomalies because GDM develops after the critical period of organogenesis (in T1)
Other Pyelonephritis/UTI: glucosuria provides a culture medium for *E. coli* and other bacteria Increased incidence of spontaneous abortion (in T1DM and T2DM, not in GDM): related to preconception glycemic control	**Labour and Delivery** PTL/prematurity: most commonly in patients with HTN/preeclampsia PTL is associated with poor glycemic control but the exact mechanism is unknown Increased incidence of stillbirth Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia
	Neonatal Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate Hyperbilirubinemia and jaundice: due to prematurity and polycythemia Hypocalcemia: exact pathophysiology not understood, may be related to functional hypoparathyroidism Polycythemia: hyperglycemia stimulates fetal erythropoietin production

Early-Onset Group B Streptococcus Disease

Epidemiology
- 15-40% recto-vaginal carrier rate

Risk Factors (for Neonatal Disease)
- <37 completed wk GA at birth
- prolonged ROM ≥18 h
- maternal intrapartum GBS colonization during current pregnancy
- GBS bacteriuria at any time during current pregnancy
- previous infant with invasive GBS disease
- maternal fever (temperature ≥38°C)

Clinical Features
- increases risk of endometritis
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia, and death)

Investigations
- offer screening to all patients at 35-37 wk GA with vaginal and anorectal swabs for GBS culture

Treatment
- prophylactic treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
- antibiotics for GBS prophylaxis (should be given 4 h prior to delivery to be considered adequate)
  - penicillin G 5 million IU IV, then 2.5 million IU IV q4 h until delivery
  - penicillin allergy but low risk for anaphylaxis: cefazolin 2 g IV, then 1 g q8 h
  - penicillin allergy and at risk of anaphylaxis: vancomycin 1 g IV q12 h or clindamycin 900 mg q8 h (only if isolate known to be susceptible to clindamycin) until delivery
  - vancomycin and clindamycin levels in amniotic fluid do not reach therapeutic levels, all babies should be screened for GBS despite treatment
- if maternal fever, broad spectrum antibiotic coverage regardless of GBS status and GA is advised
- if <37 wk GA and in labour or with ROM, IV GBS antibiotic prophylaxis for a minimum of 48 h

Indications for Intrapartum Antibiotic GBS Prophylaxis
Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines from CDC, 2010. MMWR Recomm Rep 2010;59:1-36
- Previous infant with invasive GBS disease
- GBS bacteriuria during any trimester of the current pregnancy
- Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy
- Unknown GBS status at the onset of labour (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 wk GA
  - Amniotic membrane rupture ≥18 h
  - Intrapartum temperature ≥38.0°C (≥100.4°F)
  - Intrapartum nucleic-acid amplification test positive for GBS

Urinary Tract Infection

Epidemiology
- most common medical complication of pregnancy
- asymptomatic bacteriuria in 2-7% of pregnant women, more frequently in multiparous patients
- note: asymptomatic bacteriuria should be treated in pregnancy due to increased risk of pyelonephritis and PTL

Treat asymptomatic bacteriuria in pregnancy because of increased risk of progression to cystitis, pyelonephritis, and probable increased risk of PTL

Etiology
- increased urinary stasis from mechanical and hormonal (progesterone) factors
- organisms include GBS as well as those that occur in non-pregnant patients

Clinical Features
- may be asymptomatic
- dysuria, urgency, and frequency in cystitis
- fever, flank pain, and costovertebral angle tenderness in pyelonephritis

Major organisms responsible for pyelonephritis: *E.coli, klebsiella, enterobacter, proteus*

Investigations
- urinalysis, urine C&S
- renal function tests in recurrent infections

Management
- uncomplicated UTI
  - first line: amoxicillin (250-500 mg PO q8 h x 7 d)
  - alternatives: nitrofurantoin (100 mg PO BID x 7 d) or cephalosporins
  - follow with monthly urine cultures
- pyelonephritis
  - hospitalization and IV antibiotics

Prognosis
- complications if untreated: acute cystitis, pyelonephritis, and possible PTL
- recurrence is common, offer continuous or post-coital prophylaxis with nitrofurantoin or cephalexin, except during the last 4 wk of pregnancy

Infections During Pregnancy

- infant immunity begins to develop at 9-15 wk GA
- initial response to infection is IgM production
- transplacental IgG provides passive immunity

Table 15. Infections During Pregnancy

Infection	Agent	Source of Transmission	Greatest Transmission Risk to Fetus	Effects on Fetus	Effects on Mother	Diagnosis	Management
Chicken Pox	Varicella zoster virus (herpes family)	To patient: direct, respiratory To baby: transplacental	13-30 wk GA and 5 d pre- to 2 d post-delivery	Congenital varicella syndrome (limb aplasia, chorioretinitis, cataracts, cutaneous scars, cortical atrophy, IUGR, hydrops), PTL	Fever, malaise, vesicular pruritic lesions	Clinical, ± vesicle fluid culture, ± serology	Varicella-zoster immunoglobulin (VZIG) for patient if exposed, decreases congenital varicella syndrome If maternal infection 5 d before delivery, give infant VZIG for passive immunity Note: do not administer vaccine during pregnancy (live attenuated vaccine)
***Cytomegalovirus**	DNA virus (herpes family)	To patient: blood/organ transfusion, sexual contact To baby: transplacental, during delivery, breast milk	T1-T3	5-10% develop CNS involvement (mental retardation, cerebral calcification, hydrocephalus, microcephaly, deafness, chorioretinitis)	Asymptomatic or flu-like (fever, pharyngitis, lymphadenopathy, polyarthritis)	Serologic screen; isolate virus from urine or secretion culture	No specific treatment; maintain good hygiene and avoid high-risk situations
Erythema Infectiosum (Fifth Disease)	Parvovirus B19	To patient: respiratory, infected blood products To baby: transplacental	10-20 wk GA	Spontaneous abortion (SA), stillbirth, hydrops *in utero*	Flu-like, rash, arthritis; often asymptomatic	Serology, viral PCR, maternal AFP; if IgM present, follow fetus with U/S for hydrops	If hydrops occurs, consider fetal transfusion
Hepatitis B	DNA virus	To patient: blood, saliva, semen, vaginal secretions To baby: transplacental, breast milk	T3 10% vertical transmission if asymptomatic and HBsAg +ve; 85-90% if HBsAg and HBeAg +ve	Prematurity, low birth weight, neonatal death	Fever, N/V, fatigue, jaundice, elevated liver enzymes	Serologic screening for all pregnancies	Rx neonate with HBIG and vaccine (at birth, 1, 6 mo); 90% effective

* Indicates TORCH infection

Table 15. Infections During Pregnancy

Infection	Agent	Source of Transmission	Greatest Transmission Risk to Fetus	Effects on Fetus	Effects on Mother	Diagnosis	Management
***Herpes Simplex Virus**	DNA virus	To mother: intimate mucocutaneous contact To baby: transplacental, during delivery	Delivery (if genital lesions present); less commonly *in utero*	Disseminated herpes (20%); CNS sequelae (35%); self-limited infection	Painful vesicular lesions	Clinical diagnosis	Acyclovir for symptomatic patient, suppressive therapy at 36 wk GA controversial Suggested CD if active genital lesions, even if remote from vulva
HIV	RNA retrovirus	To mother: blood, semen, vaginal secretions To baby: *in utero*, during delivery, breast milk	1/3 *in utero*, 1/3 at delivery, 1/3 breastfeeding	IUGR, PTL, PROM	See Infectious Diseases, ID24	Serology, viral PCR All pregnant women are offered screening	Triple antiretroviral therapy decreases transmission to <1% Elective CD: no previous antiviral Rx or monotherapy only, viral load unknown or >500 RNA copies/mL, unknown prenatal care, patient request
***Rubella**	ssRNA togavirus	To mother: respiratory droplets (highly contagious) To baby: transplacental	T1	SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, mitral regurgitation, IUGR, hepatitis, CNS defects, osseous changes)	Rash (50%), fever, posterior auricular or occipital lymphadenopathy, arthralgia	Serologic testing; all pregnant women screened (immune if titre >1:16); infection if IgM present or >4x increase in IgG	No specific treatment; offer vaccine following pregnancy Do not administer during pregnancy (live attenuated vaccine)
Syphilis	Spirochete (*Treponema pallidum*)	To mother: s exual contact To baby: transplacental	T1-T3	Risk of PTL, multisystem involvement, fetal death	See Infectious Diseases, ID32	VDRL screening for all pregnancies; if positive, requires confirmatory testing	Benzathine penicillin G 2.4 million IU IM x 1 dose if early syphilis, 3 doses if late syphilis, monitor VDRL monthly No approved alternatives in pregnancy; if β-lactam allergy, recommend to desensitize then treat with penicillin
***Toxoplasmosis**	Protozoa (*Toxoplasma gondii*)	To mother: raw meat, unpasteurized goat's milk, cat feces/urine To baby: transplacental	T3 (but most severe if infected in T1); only concern if primary infection during pregnancy	Congenital toxoplasmosis (chorioretinitis, hydrocephaly, intracranial calcification, mitral regurgitation, microcephaly), NB: 75% initially asymptomatic at birth	Majority subclinical; may have flu-like symptoms	IgM and IgG serology; PCR of amniotic fluid	Self-limiting in patient; spiramycin decreases fetal morbidity but not rate of transmission
Influenza	ssRNA virus	To mother: respiratory droplets To baby: transplacental	Early pregnancy	Congenital possible NTD if exposed in early pregnancy as a result of high fevers	Cough, sore throat, malaise, headaches, myalgia Complications include pneumonia	Clinical diagnosis, viral swab	Immunization with inactivated influenza vaccine If infected: symptomatic treatment, antivirals, supportive therapy

* Indicates TORCH infection

Venous Thromboembolism

Epidemiology

- incidence of 12.1 in 10000 (DVT) and 5.4 in 10000 (PE)
- increased risk of VTE throughout pregnancy (highest risk of DVT in T3) and first 3 wk of postpartum period (highest risk of PE postpartum first 6 wk)

Virchow's Triad for VTE
- Hypercoagulable state
- Venous stasis
- Endothelial damage

Risk Factors

- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, smoking, pre eclampsia, and thrombophilias (see Hematology, H36)

Table 16. Risk Factors for VTE Specific to Pregnancy

Hypercoagulability	Stasis	Endothelial Damage
Increased Factors: II, V, VII, VIII, IX, X, XII, fibrinogen Increased platelet aggregation Decreased protein S, tPA, factors XI, XIII Increased resistance to activated protein C Antithrombin can be normal or reduced	Increased venous distensibility Decreased venous tone 50% decrease in venous flow in lower extremity by T3 Uterus is mechanical impediment to venous return	Vascular damage at delivery (CD or SVD) Uterine instrumentation Peripartum pelvic surgery

Clinical Features
- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a PE are non-specific

Investigations
- duplex venous Doppler sonography for DVT
- CT angiography preferred for PE

Management
- before initiating treatment, obtain a baseline CBC including platelets and aPTT
- treatment with LMWH preferred
  - dosing varies depending on specific LMWH used
  - should be discontinued at least 24 h prior to delivery
- unfractionated heparin
  - 80 IU/kg bolus (max 5000 IU) followed by 18 IU/kg/h infusion
  - measure aPTT 6 h after the bolus
  - maintain aPTT at a therapeutic level (1.5-2x normal)
  - repeat q24 h once therapeutic
  - heparin-induced thrombocytopenia (HIT) uncommon (3%), but serious complication
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- poor evidence to support a recommendation for or against avoidance of prolonged sitting
- VTE prophylaxis
  - women on long-term anticoagulation: full therapeutic anticoagulation throughout pregnancy and for 6-12 wk postpartum
  - women with a non-active PMHx of VTE: unfractionated heparin regimens suggested
  - postpartum thromboprophylaxis should be considered if absolute risk is over 1.0%, defined as:
    - any two of the following: BMI ≥30 at first antepartum visit, smoking >10 cigarettes/d, preeclampsia, IUGR, placenta previa, emergency CD, peripartum/postpartum blood loss >1 L, any low-risk thrombophilia, maternal cardiac disease/SLE/SCD/IBD/varicose veins/GDM, preterm delivery, stillborn
    - any three or more of the following: age >35, parity ≥2, use of ART, multiple gestation, placental abruption, PROM, elective CD, maternal cancer
  - current prophylaxis regimens for acquired thrombophilias (e.g. APS) include low dose ASA in conjunction with prophylactic heparin

Normal Labour and Delivery

Definition of Labour
- true labour: regular, painful contractions of increasing intensity associated with progressive dilatation and effacement of cervix and descent of presenting part, or progression of station
  - preterm (20-36+6 wk GA)
  - term (37-41+6 wk GA)
  - postterm (≥42 wk GA)
- false labour (Braxton-Hicks contractions): irregular contractions with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any cervical dilatation, effacement, or descent
  - often relieved by rest or hydration

The Cervix
- see Bishop Score (see *Table 20, OB38*)
  - dilatation: latent phase (0-4 cm, variable time); active phase (4-10 cm)
  - effacement: thinning of the cervix by percentage or length of cervix (cm)
  - consistency: firm, medium, or soft
  - position: posterior, mid, or anterior
- other consideration
  - application: contact between the cervix and presenting part (i.e. well or poorly applied)

The Fetus
- **fetal lie**: orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, or oblique)
- **fetal presentation**: fetal body part closest to the birth canal
  - breech (complete, frank, footling and incomplete) (see *Figure 5, OB25*)
  - cephalic (vertex/occiput, face, or brow)
  - transverse (shoulder/back)
  - compound (fetal extremity prolapses along with presenting part)
  - all except vertex are considered malpresentation (see *Obstetrical Complications, OB16*)

Maternal Triage Assessment
ID: Age, GPA, EDD, GA, GBS, Rh, Serology
Chief Complaint (CC)
HPI: 4 key questions:

Activity: As much as usual, time since last movement, kick counts (lie still for 1-2 h, cold juice, feel FM – should have 6 movements in 2 h)

Bleeding: Since when, how much (pads), colour (pinky vs. brownish vs. bright red), pain, last U/S, trauma/intercourse

Contractions: Since when, how close (q x min), how long (x s), how painful

Discharge of fluid: Since when, large gush vs. trickle, soaked pants, clear vs. green vs. red, continuous

PregHx: Any complications (HTN, GDM, infections), IPS/FTS, last U/S (BPP score, growth, EFW, presentation), last vaginal exam
POBHx: Every previous pregnancy and outcome: year, SVD/CD/miscarriage/abortion, infant birthweight, length of labour, use of vacuum or forceps, complications
PMHx, Meds, Allergies, SHx
O/E: Maternal vitals, fetal heart tracing (baseline, variability, presence of accelerations/decelerations), Leopold's manoeuver, vaginal exam, U/S

- **fetal position**: position of presenting part of the fetus relative to the maternal pelvis
  - OA: most common presentation ("normal") – left OA most common
  - OP: most rotate spontaneously to OA; may cause prolonged second stage of labour
  - OT: if persistent, leads to arrest of dilatation
    - normally, fetal head enters maternal pelvis and engages in OT position
    - subsequently rotates to OA position (or OP in a small percentage of cases)
- **attitude**: flexion/extension of fetal head relative to shoulders
  - brow presentation: head partially extended (requires CD)
  - face presentation: head fully extended
    - mentum posterior always requires CD, mentum anterior can deliver vaginally
- **station**: position of presenting bony part relative to ischial spines – determined by vaginal exam
  - at ischial spines = station 0 = engaged
  - –5 to –1 cm above ischial spines
  - +1 to +5 cm below ischial spines
- **asynclitism**: alignment of the sagittal suture relative to the axis of the birth canal
  - lateral tilt seen with either anterior or posterior asynclitism and may impact descent

Reference Point for Describing Fetal Position
Occiput for cephalic presentation
Sacrum for breech presentation
Mentum for face presentation

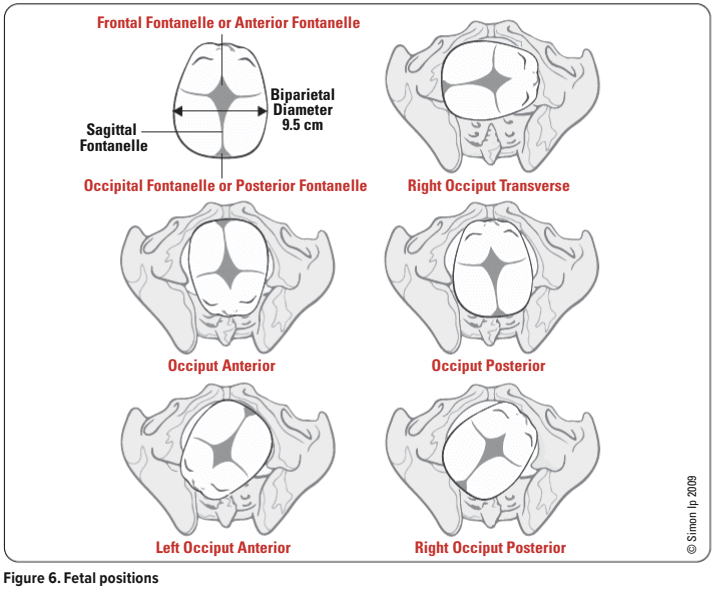


Figure 6. Fetal positions

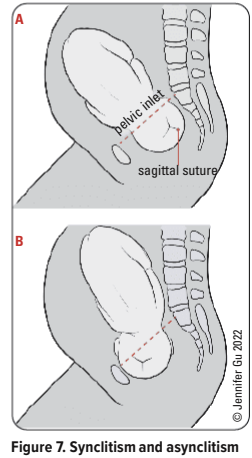


Figure 7. Synclitism and asynclitism

Four Stages of Labour

First Stage of Labour (0-10 cm cervical dilatation)

- latent phase
  - uterine contractions typically infrequent and irregular
  - slow cervical dilatation (usually to 4 cm) and effacement
- active phase
  - rapid cervical dilatation to full dilatation (nulliparous ≥1.0 cm/h, multiparous ≥1.2 cm/h)
  - phase of maximum slope on cervical dilatation curve
  - painful, regular contractions q2-3 min, lasting 45-60 s
  - contractions strongest at fundus

Second Stage of Labour (10 cm dilatation – delivery of the baby)

- from full dilatation to delivery of the baby; duration varies based on parity, contraction quality, and type of analgesia
- mother feels a desire to bear down and push with each contraction
- women may choose a comfortable position that enhances pushing efforts and delivery
  - upright (semi-sitting, squatting) and LLDP are supported in the literature
- progress measured by descent

Course of Normal Labour*

Stage	Nulliparous	Multiparous
First	6-18 h	2-10 h
Second	30 min-3 h	5-30 min
Third	5-30 min	5-30 min

*without epidural

Signs of Placental Separation
Gush of blood
Lengthening of cord
Uterus becomes globular
Fundus rises

Third Stage of Labour (delivery of the baby – delivery of the placenta)

- from baby's birth to separation and expulsion of the placenta
- can last up to 30 min before intervention is indicated
- demonstrated by gush of fresh blood, umbilical cord lengthening, uterine fundus changing shape (firm and globular), and rising upward
- active management: start oxytocin IV drip, or give 10 IU IM or 5 mg IV push, after delivery of anterior shoulder in anticipation of placental delivery, otherwise give after delivery of placenta
- routine oxytocin administration in third stage of labour can reduce the risk of PPH by >40%

Fourth Stage of Labour

- first postpartum hour
- monitor vital signs and bleeding, repair lacerations
- ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
- inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
- 3rd and 4th stages of labour most dangerous to the mother (i.e. hemorrhage)

Continuous Support for Women During Childbirth
Cochrane DB Syst Rev 2017;7:CD003766
Study: Systematic review of 27 trials from 17 countries involving a total of 15858 women.
Intervention: Continuous support vs. usual care during labour.
Outcome: Effects on mothers and their babies
Results: Women receiving continuous support were slightly more likely to have a spontaneous vaginal birth (RR 1.08, 95% CI 1.04 to 1.12) and shorter labour (mean difference -0.69 h, 95% CI -1.04 to -0.34) and were less likely to use intrapartum analgesia (RR 0.90, 95% CI 0.84 to 0.96), report dissatisfaction with their childbirth experience (RR 0.69,95% CI 0.59 to 0.79), and have a baby with a low 5 min APGAR score (RR 0.62, 95% CI 0.46 to 0.85).

The Cardinal Movements of the Fetus During Delivery

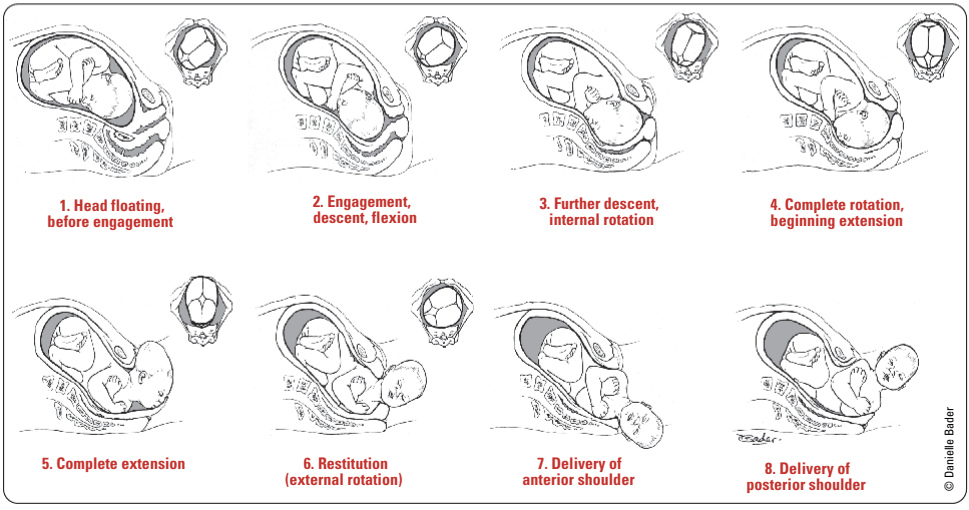

1. Head floating, before engagement
2. Engagement, descent, flexion
3. Further descent, internal rotation
4. Complete rotation, beginning extension
5. Complete extension
6. Restitution (external rotation)
7. Delivery of anterior shoulder
8. Delivery of posterior shoulder
© Danielle Bader

Figure 8. Cardinal movements of fetus during delivery
Adapted from illustration in Williams Obstetrics, 19th ed

Analgesic and Anesthetic Techniques in Labour and Birth

- pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

Non-Pharmacologic Pain Relief Techniques

- reduction of painful stimuli
  - maternal movement, position change, counter-pressure, and abdominal compression
- activation of peripheral sensory receptors
  - superficial heat and cold
  - immersion in water during labour
  - touch and massage, acupuncture, and acupressure
  - TENS
  - intradermal injection of sterile water in skin over sacrum
  - aromatherapy
- enhancement of descending inhibitory pathways
  - attention focusing and distraction
  - hypnosis
  - music and audio analgesia
  - biofeedback

Pharmacologic Methods (see Anesthesia, A27)
- nitrous oxide (e.g. self-administered Entonox®)
- narcotics (usually combined with anti-emetic)
- pudendal nerve block
- perineal infiltration with local anesthetic
- regional anesthesia (epidural block, combined spinal-epidural, and spinal)

Fetal Monitoring in Labour

- see online **Fetal Heart Rate Tutorial**

Vaginal Exam
- membrane status, as indicated by amniotic fluid (clear, pink, bloody, and meconium)
- cervical effacement (thinning), dilatation, consistency, position, and application
- fetal presenting part, position, and station
- bony pelvis size and shape
- monitor progress of labour at regular intervals and document in a partogram

Intrapartum Fetal Monitoring
- intermittent fetal auscultation with Doppler device q15-30 min for 1 min in active phase of first stage following a contraction, q5 min during second stage when pushing has begun
- continuous electronic FHR monitoring reserved for abnormal auscultation, prolonged labour, labour which is induced or augmented, meconium present, multiple gestation/fetal complication, and concerns about the fetus tolerating labour
  - use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate when used routinely in all patients (i.e. no risk factors)
  - techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
- fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (CTG) to resolve the interpretation of abnormal or atypical patterns

Electronic FHR Monitoring
- FHR measured by Doppler; contractions measured by tocometer
- described in terms of baseline FHR, variability (short-term, long-term), and periodicity (accelerations, decelerations)
- see *Table 5, OB10*
- **Baseline FHR**
  - normal range is 110-160 bpm
  - parameter of fetal well-being vs. distress
- **Variability**
  - physiologic variability is a normal characteristic of FHR
  - variability is measured over a 15 min period and is described as: absent, minimal (<6 bpm), moderate (6-25 bpm), or marked (>25 bpm)
  - normal variability indicates fetal acid-base status is acceptable
  - can only be assessed by electronic contraction monitoring (CTG)
  - variability decreases intermittently even in a healthy fetus
- **Periodicity**
  - accelerations: increase of ≥15 bpm for ≥15 s (or ≥10 bpm for ≥10 s if <32 wk GA)
  - decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability, see *Table 18, OB37*

Table 17. Factors Affecting Fetal Heart Rate

	Fetal Tachycardia (FHR >160 bpm)	Fetal Bradycardia (FHR <110 bpm)	Decreased Variability
Maternal Factors	Fever, hyperthyroidism, anemia, dehydration	Hypothermia, hypotension, hypoglycemia, position, umbilical cord occlusion	Infection Dehydration
Fetal Factors	Arrhythmia, anemia, infection, prolonged activity, chronic hypoxemia, congenital anomalies	Rapid descent, dysrhythmia, heart block, hypoxia, vagal stimulation (head compression), hypothermia, acidosis	CNS anomalies Dysrhythmia Inactivity/sleep cycle, preterm fetus
Drugs	Sympathomimetics	β-blockers Anesthetics	Narcotics, sedatives Magnesium sulphate, β-blockers
Uteroplacental	Early hypoxia (abruption, HTN) Chorioamnionitis	Late hypoxia (abruption, HTN) Acute cord prolapse Hypercontractility	Hypoxia

Approach to the Management of Abnormal FHR

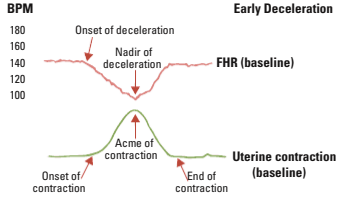
POISON – ER
Position (LLDP)
O$_2$ (100% by mask)
IV fluids (corrects maternal hypotension)
Fetal scalp stimulation, fetal scalp electrode, fetal scalp pH
Stop oxytocin
Notify physician
Vaginal exam to rule out cord prolapse
Rule out fever, dehydration, drug effects, and prematurity
- If above fails, consider CD

Continuous Cardiotocography (CTG) as a Form of Electronic Fetal Monitoring (EFM) for Fetal Assessment During Labour
Cochrane DB Syst Rev 2017;5:CD006066
Purpose: To examine the effectiveness of continuous electronic fetal monitoring or cardiotocography during labour
Selection Criteria: Randomized and quasi-randomized controlled trials comparing continuous CTG (with and without fetal blood sampling) to a) no fetal monitoring, b) intermittent auscultation, or c) intermittent CTG
Results: 13 trials, 37000 women. Continuous CTG compared with intermittent auscultation showed no difference in overall perinatal death rate or cerebral palsy rates. Nonetheless, neonatal seizures were halved (RR 0.50, 95% CI 0.31-0.80) and there was a significant increase in CD (RR 1.63, 95% CI 1.29-2.07) and instrumental vaginal birth (RR 1.15, 95% CI 1.01-1.33) with CTG
Conclusion: Continuous CTG may reduce the incidence of neonatal seizures, but has no effect on cerebral palsy rates, infant mortality, or other measures of neonatal well-being. Continuous CTG was also associated with an increase in CD and instrumental deliveries

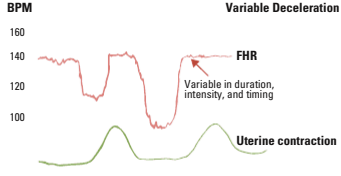
Table 18. Comparison of Decelerations

Comparisons

Early Decelerations
- Uniform shape with onset early in contraction, returns to baseline by end of contraction, mirrors contraction (nadir occurs at peak of contraction)
- Gradual deceleration and return to baseline
- Often repetitive; no effect on baseline FHR or variability
- Benign, due to vagal response to head compression

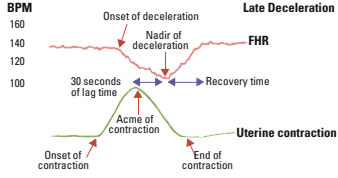


Variable Decelerations
- Variable in shape, onset, and duration
- Most common type of periodicity seen during labour
- Often with abrupt drop in FHR >15 bpm below baseline (>15 s, <2 min); usually no effect on baseline FHR or variability
- Due to cord compression or, in second stage, forceful pushing with contractions



Complicated Variable Decelerations
- FHR drop <60 bpm for >60 s
  - Loss of variability or decrease in baseline after deceleration
  - Biphasic deceleration
  - Slow return to baseline
  - Baseline tachycardia or bradycardia
  - May be associated with fetal acidemia

Late Decelerations
- Uniform shape with onset, nadir, and recovery occurring after peak of contraction, slow return to baseline
- May cause decreased variability and change in baseline FHR
- Due to fetal hypoxia and acidemia, maternal hypotension, or uterine hypertonus
- Usually a sign of uteroplacental insufficiency (an ominous sign)



Rule of 60s Suggesting Severe Variable Decelerations
Deceleration to <60 bpm
>60 bpm below baseline
>60 s in duration with slow return to baseline

Fetal Scalp Blood Sampling
- cervix must be adequately dilated
- indicated when atypical or abnormal FHR is suggested by clinical parameters including heavy meconium or abnormal FHR patterns (including unexplained low variability, repetitive late decelerations, complex variable decelerations, and fetal cardiac arrhythmias)
- done by measuring pH or more recently fetal lactate
  - pH ≥7.25, lactate <4.2 mmol/L: normal, repeat if abnormal FHR persists
  - pH 7.21-7.24, lactate 4.2-4.8 mmol/L: repeat assessment in 30 min or consider delivery if rapid fall since last sample
  - pH ≤7.20, lactate >4.8 mmol/L indicates fetal acidosis, delivery is indicated
- contraindications:
  - known or suspected fetal blood dyscrasia (hemophilia, VWD)
  - active maternal infection (HIV, genital herpes, Hep B)

Fetal Oxygenation
- uterine contractions during labour decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow with no adverse effects
- fetal response to hypoxia/asphyxia:
  - decreased movement, tone, and breathing activities
  - anaerobic metabolism (decreased pH)
  - transient fetal bradycardia followed by fetal tachycardia
  - redistribution of fetal blood flow
- increased flow to brain, heart, and adrenals
- decreased flow to kidneys, lungs, gut, liver, and peripheral tissues
- increase in fetal blood pressure

Table 19. Factors Affecting Fetal Oxygenation

Factor	Mechanism	Example
Maternal	Decreased maternal oxygen carrying capacity	Significant anemia (iron deficiency, hemoglobinopathies), carboxyhemoglobin (smokers)
	Decreased uterine blood flow	Hypotension (blood loss, sepsis), regional anesthesia, maternal positioning
	Chronic maternal conditions	Vasculopathies (SLE, T1DM, chronic HTN), APS, cyanotic heart disease, COPD
Uteroplacental	Uterine hypertonus	Placental abruption, tachysystole secondary to oxytocin, prostaglandins, or normal labour
	Uteroplacental dysfunction	Placental abruption, placental infarction (dysfunction marked by IUGR, oligohydramnios, abnormal Doppler studies), chorioamnionitis, placental edema (DM, hydrops), placental senescence (post-dates)
Fetal	Cord compression	Oligohydramnios, cord prolapse, or entanglement
	Decreased fetal oxygen carrying capacity	Significant anemia (isoimmunization, fetomaternal bleed), carboxyhemoglobin (exposure to smokers)

Induction and Augmentation of Labour

Induction of Labour

Definition

- artificial initiation of labour in a pregnant patient prior to spontaneous initiation to deliver the fetus and placenta

Prerequisites for Labour Induction

- capability for CD if necessary
- maternal:
  - favourable: soft, effaced (thinned), anterior position, dilated
  - if cervix is not favourable, use prostaglandin vaginal insert (Cervidil®), prostaglandin gel (Prepidil®), misoprostol (Cytotec®), or mechanical induction (Foley/Cooks catheter)
- fetal:
  - normal fetal heart tracing
  - cephalic presentation
  - adequate fetal monitoring available
- likelihood of success determined by Bishop score:
  - cervix considered unfavourable if ≤3
  - cervix favourable if ≥6
  - score of 9-13 associated with high likelihood of vaginal delivery

Table 20. Bishop Score

Cervical Characteristic	0	1	2	3
Position	Posterior	Mid	Anterior	–
Consistency	Firm	Medium	Soft	–
Effacement (%)	0-30	40-50	60-70	≥80
Dilatation (cm)	0	1-2	3-4	≥5
Station of Fetal Head	-3	-2	-1, 0	+1, +2, +3

Indications

- late term (40-41 wk GA) and postterm pregnancy (≥42 wk GA) = most common reason for induction
- 39-40 wk GA especially with risk factors such as advanced maternal age (>40 yr): consideration should be given to IOL due to increased risk of stillbirth
- >41 wk GA: offer IOL if vaginal delivery is not contraindicated
  - IOL shown to decrease CD, FHR changes, meconium staining, macrosomia, and death when compared with expectant management
- >41 wk GA and expectant management elected: serial fetal surveillance
  - FM count by the mother
  - BPP q3-4 d
- maternal indications for induction:
  - DM = second most common reason for induction
  - gestational HTN ≥38 wk GA
  - preeclampsia ≥37 wk GA
  - other maternal medical comorbidities, (e.g. renal or lung disease, chronic HTN, and cholestasis)
  - significant but stable antepartum hemorrhage
  - labour induction may be offered to patients age ≥40 at ≥39 wk GA due to increased risk of stillbirth

Induction is indicated when the risk of continuing pregnancy exceeds the risks associated with induction of labour and delivery

Induction vs. Augmentation
Induction is the artificial initiation of labour
Augmentation promotes contractions when spontaneous contractions are inadequate

Consider the Following Before Induction

Indication for induction
Contraindications
GA
Cervical favourability
Fetal presentation
Potential for CPD
Fetal well-being/FHR
Membrane status

- maternal-fetal indications for induction:
  - isoimmunization, PROM, and chorioamnionitis
- fetal indications for induction:
  - suspected fetal compromise as evidenced by biochemical or biophysical indications
  - macrosomia, fetal demise, IUGR, oligo/polyhydramnios, anomalies requiring surgical intervention, and twins
  - previous stillbirth or low PAPP-A

Risks
- failure to achieve labour and/or vaginal birth
- tachysystole with fetal compromise or uterine rupture
- maternal side effects to medications
- uterine atony and PPH if labour is prolonged

Contraindications
- maternal
  - any contraindication to vaginal delivery (prior classical or inverted T-incision CD or uterine surgery (e.g. myomectomy))
  - unstable maternal condition
  - active maternal genital herpes
  - invasive cervical carcinoma
  - pelvic structure deformities
  - previous uterine rupture
- maternal-fetal
  - placenta previa or vasa previa
  - cord prolapse or cord presentation
- fetal
  - fetal distress (i.e. abnormal FHR tracing) or malpresentation

Methods for Induction of Labour

CERVICAL RIPENING

Definition
- use of medications or other means to soften, efface, and dilate the cervix; increases likelihood of successful induction
- ripening of an unfavourable cervix (Bishop score <6) is warranted prior to IOL

Methods
- Foley catheter placement to mechanically dilate the cervix: first-line when feasible
- intravaginal PGE2 gel (Prostin® gel): long and closed cervix
  - recommended dosing: q6-12 h up to 3 doses
- intravaginal PGE2 (Cervidil®): long and closed cervix, may use if ROM
  - continuous release, can be removed if needed
  - controlled release PGE2
- intracervical PGE2 (Prepidil®)
- intravaginal PGE1 misoprostol (Cytotec®): long and closed cervix
  - inexpensive, stored at room temperature
  - more effective than PGE2 for achieving vaginal delivery and less epidural use
  - contraindicated in the third trimester with previous caesarean delivery

INDUCTION OF LABOUR

Amniotomy
- artificial ROM (amniotomy) to stimulate prostaglandin synthesis and secretion; may try this as initial measure if cervix is dilated and soft, the membranes can be felt, and if the head is well applied to the cervix
- few studies address the value of amniotomy alone for IOL
- amniotomy plus IV oxytocin: more patients delivered vaginally at 24 h than amniotomy alone (RR=0.03) and had fewer instrumental vaginal deliveries (RR=5.5)

Oxytocin
- oxytocin (Pitocin®): 10 U in 1 L normal saline, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60 min
- reduces rate of unsuccessful vaginal deliveries within 24 h when used alone (8.3% vs. 54%, RR=0.16)
- ideal dosing regimen of oxytocin is not known
- current recommendations: use the minimum dose to achieve active labour and increase q30 min as needed
- reassessment should occur once a dose of 20 mU/min is reached
- caution is needed in patients with previous CD or uterine surgery

Evidence for Cervical Ripening Methods (SOGC Guidelines)
- Meta-analysis of five trials has concluded that the use of oxytocin to ripen the cervix is not effective
- Since the best dose and route of misoprostol for labour induction with a live fetus are not known and there are concerns regarding hyperstimulation, the use of misoprostol for IOL should be in cases of IUFD to initiate labour

Vaginal Prostaglandin (PGE2 and PGF2a) for Induction of Labour at Term
Cochrane DB Syst Rev 2014;6:CD003101
This analysis examined the results of 70 RCTs (n=11487 women). Use of vaginal PGE2 increased the risk of uterine hyperstimulation with FHR changes (RR 3.16; 95% CI 1.67-5.98) and likely reduces the CD rate slightly (RR 0.91; 95% CI 0.81-1.02) compared to placebo or no treatment. There were no detectable differences in effectiveness between gel or tablet forms of PGE2 or between sustained release pessaries and PGE2 gel/tablets
Theoretical advantages between intravaginal PGE2 (Cervidil®) compared to Intravaginal Prostaglandin Gel:
- Slow, continuous release
- Ability to use oxytocin 30 min after removal vs. 6 h for gel
- Ability to remove insert if required (e.g. excessive uterine activity)

Labour Induction vs. Expectant Management in Low-Risk Nulliparous Women
NEJM 2018;379:513-523
Purpose: To assess whether induction of labour between 39+0 wk GA and 40+6 wk GA improves perinatal and maternal outcomes
Methods: 6106 low-risk nulliparous women were randomized to the elective induction or the expectant management groups. The primary outcome was a composite outcome of perinatal death or severe neonatal complications. The main secondary outcome was the rate of CD
Results: The primary perinatal outcome occurred in 4.3% of neonates from the elective induction group and 5.4% of neonates from the expectant management group (RR: 0.80; 95% CI: 0.64-1.00; P=0.049, P<0.046 for significance). This result was consistent after adjusting for other maternal factors. CD occurred in 18.6% of induction group mothers compared to 22.3% of expectant management group mothers (RR: 0.84; 95% CI: 0.76-0.93, P<0.001). There were no significant differences in primary or secondary outcomes in subgroup analyses
Conclusion: Elective induction of labour between 39+0 and 41+0 wk GA did not result in increased incidence of adverse perinatal outcomes and resulted in fewer CDs

Oxytocin t½ = 3-5 min

- no earlier than:
  - 30 min post intravaginal PGE2 removal
  - 6 h post intravaginal PGE2 gel insertion
  - 4 h post intravaginal PGE1 insertion
- potential complications
  - tachysystole/tetanic contraction (may cause fetal distress or uterine rupture)
  - uterine muscle fatigue, uterine atony (may result in PPH)
  - vasopressin-like action causing anti-diuresis

Augmentation of Labour

- augmentation of labour with amniotomy and/or oxytocin may be used to promote stronger and more frequent contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur

Provided there are no contraindications, oxytocin is used to improve uterine contraction strength and/or frequency

Abnormalities and Complications of Labour and Delivery

Abnormal Progression of Labour (Dystocia)

Definition
- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labour
- during active phase: >2 h of <1 cm/h
- during 2nd stage: >1 h with no descent during active pushing

Etiology
- power (leading cause): contractions (hypotonic, uncoordinated), inadequate maternal expulsive efforts
- passenger: fetal position, attitude, size, anomalies (e.g. hydrocephalus)
- passage: pelvic structure (CPD), maternal soft tissue factors (tumours, full bladder or rectum, vaginal septum)
- psyche: hormones released in response to stress may contribute to dystocia; psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed
- practitioner: understanding and expectations of normal labour progress individualized for patient

The 5 Ps of Dystocia
Power
Passenger
Passage
Psyche
Practitioner

Management
- confirm diagnosis of labour (rule out false labour)
- search for evidence of CPD
- concern for dystocia if adequate contractions measured by intrauterine pressure catheter with no descent/dilatation for >2 h
- management: if CPD ruled out, IV oxytocin augmentation ± amniotomy, optimize fetal position, optimize pain control

Risks of Dystocia
- inadequate progression of labour is associated with an increased incidence of:
  - maternal stress
  - maternal infection
  - PPH
  - need for neonatal resuscitation
  - fetal compromise (from tachysystole)
  - uterine rupture
  - hypotension

Shoulder Dystocia

Definition
- fetal anterior shoulder impacted above pubic symphysis after fetal head has been delivered
- life threatening emergency

Etiology/Epidemiology
- incidence 0.2-3% of deliveries
- occurs when breadth of shoulders is greater than biparietal diameter of the head

Risk Factors
- maternal: obesity, DM, multiparity, and previous shoulder dystocia
- fetal: prolonged gestation or macrosomia (especially if associated with GDM)
- labour:
  - prolonged 2nd stage
  - instrumental midpelvic delivery

Presentation
- "turtle sign": head delivered but retracts against perineum
- complications:
  - fetal:
    - hypoxic ischemic encephalopathy (chest compression by vagina or cord compression by pelvis can lead to hypoxia)
    - brachial plexus injury (Erb's palsy: C5-C7; Klumpke's palsy: C8-T1), 90% partially resolve within 6 mo
    - fracture (clavicle, humerus, and cervical spine)
    - death
  - maternal:
    - perineal injury
    - PPH (uterine atony or lacerations)
    - uterine rupture

Treatment
- goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved (see sidebar)
- other last line options:
  - cleidotomy (deliberate fracture of neonatal clavicle)
  - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent CD
  - symphysiotomy

Prognosis
- 1% risk of long-term disability for infant

Approach to the Management of Shoulder Dystocia

ALARMER
Ask for help
Legs in full flexion (McRoberts maneuver)
Anterior shoulder disimpaction (suprapubic pressure)
Release posterior shoulder by rotating it anteriorly with hand in the vagina under adequate anesthesia
Manual corkscrew i.e. rotate the fetus by the posterior shoulder until the anterior shoulder emerges from behind the maternal symphysis
Episiotomy
Rollover (on hands and knees)

*Note that suprapubic pressure and McRoberts maneuver together will resolve 90% of cases

Umbilical Cord Prolapse

Definition
- descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

Etiology/Epidemiology
- increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, and CPD
- incidence: 0.16-0.18% of deliveries

Presentation
- visible or palpable cord
- FHR changes (variable decelerations, bradycardia, or both)

Treatment
- emergency CD if not fully dilated and vaginal delivery not imminent
- O_2 to mother, monitor FHR
- keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
- intrauterine resuscitation by alleviating pressure of the presenting part on the cord
  - manually elevate fetal head with a pelvic exam
  - place patient in steep Trendelenburg or knee-to-chest position
  - retrofilling the bladder with 500-700 mL of normal saline
- if fetal demise or too premature (<22 wk GA), allow labour and delivery

Umbilical Cord Accident Causes
- Nuchal cord
- Type A (looped)
- Type B (hitched)
- Body loop
- Single artery
- True knot
- Torsion
- Velamentous cord insertion
- Short cord <35 cm
- Long cord >80 cm

1/3 of protraction disorders develop into 2° arrest of dilatation due to CPD

2/3 of protraction disorders progress through labour to vaginal delivery

Uterine Rupture

Definition
- associated with previous uterine scar (in 40% of cases), tachysystole with oxytocin, grand multiparity, and previous intrauterine manipulation
- generally occurs during labour, but can occur earlier with a classical incision
- 0.5-0.8% incidence, up to 12% with classical incision

Risk Factors
- uterine scarring (e.g. previous uterine surgeries including CD (especially classical incision), perforation with D&C, and myomectomy)
- excessive uterine stimulation (e.g. protracted labour, oxytocin, and prostaglandins)
- uterine trauma (e.g. operative equipment, ECV)
- multiparity
- uterine abnormalities
- malpresentation
- placenta accreta

Presentation
- prolonged fetal bradycardia (most common presentation)
- acute onset of constant lower abdominal pain, may not have pain if receiving epidural analgesia
- hyper/hypotonic uterine contractions
- abnormal progress in labour
- vaginal bleeding
- intra-abdominal hemorrhage
- loss of station of the presenting fetal part
- maternal tachycardia, hypotension, or shock

Treatment
- rule out other causes (i.e. placental abruption)
- maternal stabilization (may require hysterectomy), treat hypovolemia
- immediate delivery for fetal survival

Complications
- maternal mortality 1-10%
- maternal hemorrhage, shock, DIC
- amniotic fluid embolus
- hysterectomy if uncontrollable hemorrhage
- fetal distress, associated with infant mortality as high as 15%

Maternal Mortality Causes
- Thromboembolism
- Cardiac event
- Suicide
- Sepsis
- Ectopic pregnancy
- HTN
- Amniotic fluid embolism
- Hemorrhage

*In Canada (2013), lifetime risk of maternal death is 1/5200

Amniotic Fluid Embolism

Definition
- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

Etiology/Epidemiology
- rare intrapartum or immediate postpartum complication
- 13-30% maternal mortality rate
- leading cause of maternal death in induced abortions and miscarriages
- 1 in 8000 to 1 in 80000 births

Risk Factors
- placental abruption
- rapid labour
- multiparity
- uterine rupture
- uterine manipulation
- induction medication and procedures

Differential Diagnosis
- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruption, and chronic coagulopathy

Presentation
- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia), and coagulopathy
- seizure in 10%
- ARDS and left ventricular dysfunction seen in survivors
- aura in up to one-third of patients

Management
- should be managed in the ICU by a multidisciplinary team
- supportive measures (high flow O_2, ventilation support, fluid resuscitation, inotropic support, ± intubation) and coagulopathy correction

Chorioamnionitis

Definition
- infection of the chorion, amnion, and amniotic fluid

Etiology/Epidemiology
- incidence: 1-5% of term pregnancies and up to 25% in preterm deliveries
- ascending infection (microorganisms from vagina)
- predominant microorganisms include: GBS, *Bacteroides* and *Prevotella* species, *E. coli*, and anaerobic *Streptococcus*

Risk Factors
- low parity, prolonged ROM, long labour, multiple vaginal exams during labour, and internal monitoring
- bacterial vaginosis and other vaginal infections

Clinical Features
- diagnostic feature: maternal fever (one-time measurement of ≥39°, or persistent fever of ≥38° for >30 min), fetal tachycardia, foul and purulent cervical discharge
- non-specific features: maternal tachycardia, uterine tenderness

Clinical Features of Chorioamnionitis

Temperature
Tachycardia (maternal or fetal)
Tenderness (uterine)
Foul discharge

Investigations
- CBC: leukocytosis, elevated serum lactate
- amniotic fluid: Gram stain, glucose, or culture results consistent with infection

Treatment
- IV antibiotics
  - ampicillin 2 g IV q6 h + gentamicin 2 mg/kg load, then 1.5 mg/kg IV q8 h
  - anaerobic coverage (i.e. clindamycin 900 mg IV q8 h)
  - if at risk for endometritis, continue treatment postpartum especially if CD
- antipyretics
- proper labour progression (not an indication for immediate delivery or CD, especially if delivery is imminent and can be done safely)

Complications
- bacteremia of mother or fetus, wound infection if CD, pelvic abscess, neonatal meningitis, maternal or neonatal sepsis, and neonatal death
- long-term infant complications: cerebral palsy and bronchopulmonary dysplasia

Meconium

Epidemiology
- present early in labour in 10% of pregnancies, more common in postterm pregnancies
- in general, meconium may be present in up to 25% of all labours; usually NOT associated with poor outcome
- concern if fluid changes from clear to meconium-stained
- always abnormal if seen in preterm fetus

Particulate (thickened) meconium is associated with lower APGARs, an increased risk of meconium aspiration, and perinatal death. Particulate meconium generally has a darker green or black colour, whereas thin meconium is usually yellow to light green

Etiology
- likely cord compression ± uterine hypertonia
- may indicate undiagnosed breech
- increasing meconium during labour may be a sign of fetal distress

Features
- may be watery or thicker (particulate)
- light yellow-green or dark green-black in colour

Treatment
- call respiratory therapy, neonatology, or pediatrics to delivery room
- closely monitor FHR for signs of fetal distress

Operative Obstetrics

Operative Vaginal Delivery

Definition
- forceps or vacuum extraction

Indications
- fetal:
  - atypical or abnormal FHR tracing, evidence of fetal compromise
  - consider if second stage is prolonged, as this may be due to poor contractions or failure of fetal head to rotate
- maternal:
  - need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
  - exhaustion, lack of cooperation, and excessive analgesia may impair pushing effort

Prerequisites for Operative Vaginal Delivery

ABCDEFGHIJK
Anesthesia (adequate)
Bladder empty
Cervix fully dilated and effaced with ROM
Determine position of fetal head
Equipment ready (including facilities for emergent CD)
Fontanelle (posterior fontanelle midway between thighs)
Gentle traction
Handle elevated
Incision (episiotomy)
Once jaw visible remove forceps
Knowledgeable operator

Contraindications
- cervix not fully dilated
- membranes intact
- unknown fetal head position
- unengaged head
- fetal bone demineralization disorder (e.g. osteogenesis imperfecta)
- fetal bleeding disorder (e.g. hemophilia or VWD)
- brow or face presentation

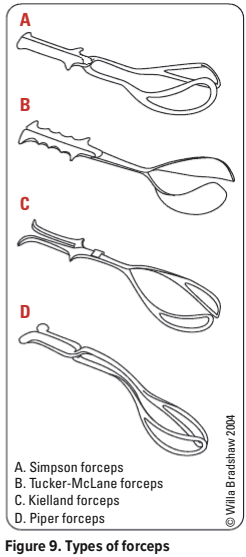
Forceps

Outlet Forceps
- head visible between labia in between contractions
- sagittal suture in or close to AP diameter
- rotation cannot exceed 45°

Low Forceps
- presenting part at station +2 cm or greater
- subdivided based on whether rotation less than or greater than 45°

Mid Forceps
- presenting part below spines but above station +2 cm

Types of Forceps
- Simpson or Tucker-McLane forceps for OA presentations
- Kielland (rotational) forceps when rotation of head or correction of asynclitism is required
- Piper forceps for after-coming head in breech delivery
- Wrigley's for preterm babies



A. Simpson forceps
B. Tucker-McLane forceps
C. Kielland forceps
D. Piper forceps

Figure 9. Types of forceps

Vacuum Extraction

- traction instrument used as alternative to forceps delivery; aids maternal pushing
- contraindications: <34 wk GA (<2500 g), fetal head deflexed, fetus requires rotation, fetal condition (e.g. bleeding disorder)

Table 21. Advantages and Disadvantages of Forceps vs. Vacuum Extraction

	Forceps	Vacuum Extraction
Advantages	Higher overall success rate for vaginal delivery Decreased incidence of fetal morbidity	Easier to apply Less anesthesia required Less maternal soft tissue injury compared to forceps
Disadvantages	Greater incidence of maternal injury	Suitable only for vertex presentations Contraindicated in preterm delivery
Complications	Maternal: cervical/vaginal/perineal lacerations including OASIS, injury to bladder, uterus, or bone, pelvic nerve damage, PPH, and infections Fetal: fractures, facial nerve palsy, trauma to face/scalp, intracerebral hemorrhage, cephalohematoma, and cord compression	Maternal: perineal lacerations/OASIS, PPH, and infection Fetal: cephalohematoma, retinal hemorrhages, and jaundice (increased compared to forceps), Subgaleal hemorrhage Subaponeurotic hemorrhage Soft tissue trauma

Perineal Lacerations

- 1st degree: involves skin and vaginal mucosa but not underlying fascia and muscle
- 2nd degree: involves fascia and muscles of the perineal body but not the anal sphincter
- 3rd degree: involves the anal sphincter (3A: <50% of external anal sphincter; 3B: >50% of external anal sphincter; 3C: external and internal anal sphincters)
- 4th degree: extends through the anal sphincter complex (external and internal) and into the rectal mucosa
- for 3rd and 4th-degree tears:
  - a single prophylactic dose of IV antibiotics (2nd generation cephalosporin, e.g. cefoxitin or cefotetan) should be administered to reduce perineal wound complications
  - laxatives should also be prescribed and constipation should be avoided
  - recommend postpartum pelvic physiotherapy and endoanal U/S to assess integrity of anal sphincters 3-4 mo post repair

Limits for Trial of Vacuum

After 3 pulls over 3 contractions with no progress

After 3 pop-offs with no obvious cause

20 min and delivery is not imminent

Risk Factors for the Development of Obstetric Anal Sphincter Injuries in Modern Obstetric Practice

Obstet Gynecol 2018;131:290-296

Purpose: To characterize the rate of obstetric anal sphincter injuries and identify risk factors of obstetric anal sphincter injuries, including duration of the second stage of labour

Methods: Retrospective cohort study including all singleton, term, cephalic vaginal deliveries from 2013 to 2014

Results: The overall incidence rate of obstetric anal sphincter injuries was 4.9% (3.6% of women who delivered spontaneously vs. 24.0% of women who had a vacuum-assisted vaginal delivery, P<0.001, 95% CI 18.1–22.6%). Further analyses suggested that incidence was higher among women with second stage of labour longer than 2 h, Asian race, nulliparity, VBAC, episiotomy, and vacuum delivery. Women with a vacuum-assisted vaginal delivery had four times the odds of obstetric anal sphincter injury (adjusted odds ratio = 4.23, 95% CI 3.59-4.98) and those whose second stage of labour lasted at least 180 min vs. less than 60 min had three times the odds of injury (adjusted odds ratio = 3.20, 95% CI 2.62-3.89)

Conclusion: Vacuum-assisted vaginal delivery had the highest odds of obstetric anal sphincter injury followed by prolonged second stage of labor. Risk factors should be used to guide decision-making

Episiotomy

Definition
- incision in the perineal body at the time of delivery
- essentially a controlled 2nd degree laceration
- midline: incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernosus muscles
  - heals better, but increases risk of extension into a 3rd/4th degree tear
- mediolateral: incision through bulbocavernosus, superficial transverse perineal muscle, and levator ani, 60° angle from midline
  - reduces risk of extensive tear, but more painful

Indications
- to relieve obstruction of the unyielding perineum
- to expedite delivery (e.g. abnormal FHR pattern)
- instrumental delivery
- controversial between practitioners as to whether it is preferable to make an episiotomy or let the perineum tear as neede
- current evidence suggests letting perineum tear and then repair as needed (restricted use)

Complications
- infection, hematoma, pain, extension into anal musculature or rectal mucosa, fistula formation, and incontinence

Common OR Questions

7 Layers to Dissect
Skin, fatty layer, fascia, muscle separation (rectus abdominis), peritoneum, bladder flap, uterus

Layers of the Rectus Sheath
Above the arcuate line: anterior rectus sheath (aponeurosis of external oblique, anterior internal oblique), rectus abdominis, posterior rectus sheath (aponeurosis of posterior internal internal oblique, transversus abdominis)
Below the arcuate line: aponeurosis of external oblique, internal oblique, transversus abdominis (all anterior)

Name of the Obliterated Umbilical Ligament
Urachus

Most CDs are performed with regional analgesia

Caesarean Delivery

Epidemiology
- overall 28% rate in Canada (range 18.5-35.3% by province/territory)

Indications
- maternal: obstruction of descent (e.g. maternal fibroids), active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery (past CD is most common), and underlying maternal illness (eclampsia, HELLP syndrome, heart disease)
- maternal-fetal: failure to progress, placental abruption or previa, and vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, certain congenital anomalies, and multiple gestation

Types of Caesarean Incisions
- skin
  - **transverse (e.g. Pfannenstiel or Joel-Cohen)**
    - decreased abdominal exposure
    - improved strength and cosmesis
    - reduced pain
  - vertical midline
    - rapid peritoneal entry and increased exposure (e.g. obstruction due to large fibroids)
    - increased dehiscence
- uterine
  - **low transverse**: in non-contractile lower segment
    - decreased chance for rupture in subsequent pregnancies
  - low vertical
    - used for very preterm infants or poorly developed maternal lower uterine segment
  - classical (rare): in thick, contractile segment
    - used for transverse lie with fetal back down, preterm breech, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid, and inaccessible lower uterine segment (e.g. morbid obesity)

Risks/Complications
- anesthetic complications (e.g. aspiration)
- hemorrhage (average blood loss ~1000 mL)
- infection (UTI, wound, and endometritis)
  - single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g IV)
- injury to surrounding structures (bowel, bladder, ureter, and uterus)
- thromboembolism (DVT, PE)
- increased recovery time/hospital stay
- maternal mortality (<0.1%)
- subsequent placenta accreta spectrum

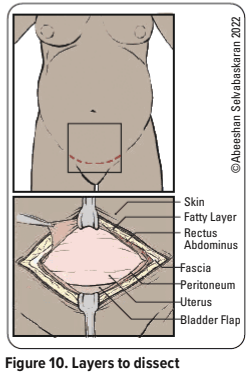


Figure 10. Layers to dissect

Trial of Labour after Caesarean (TOLAC)

- should be recommended if no contraindications after previous low transverse incision
- success rate varies with indication for previous CD (generally 60-80%)
- risk of uterine rupture (0.47% with low transverse incision), increased by interval <18 mo and oxytocin administration

Contraindications
- previous classical, inverted T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
- any contraindication to vaginal birth (e.g. placenta previa)
- inadequate facilities or personnel for emergency CD

TOLAC*
- Rate of successful TOLAC ranges from 60-82%
- Relative risk of maternal death is higher for elective repeat CD
- Relative risk of uterine rupture, composite serious maternal morbidity, and fetal death is higher for TOLAC
- Absolute risk of above outcomes is low for both CD and TOLAC
- Limited evidence in comparative data between TOLAC and repeat CD

*SOGC guideline No. 382 - Trial of Labour After Caesarean. JOGC 2019; 41: 992-1011

Postpartum Period Complications

- puerperium: 6 wk period of adjustment after pregnancy-induced anatomic and physiologic changes are reversed

Postpartum Hemorrhage

Definition
- loss of >1000 mL of blood after CD, >500 mL of blood after vaginal delivery, or bleeding associated with signs/symptoms of hypovolemia within 24 h of birthing process regardless of mode of delivery
- primary – within first 24 h postpartum
- secondary – after 24 h but within first 12 wk

Uterine atony is the most common cause of PPH

Epidemiology
- incidence 5-15%

Etiology (4 Ts)
1. Tone (uterine atony)
- most common cause of PPH (>80%)
- avoid with active management of 3rd stage of labour with 1) oxytocin administration; 2) uterine massage; and 3) umbilical cord traction for delivery of the placenta
- due to:
  - overdistended uterus (polyhydramnios, multiple gestations, and macrosomia)
  - uterine muscle exhaustion (prolonged or rapid labour, grand multiparity, oxytocin use, and general anesthetic)
  - uterine distortion (fibroids)
  - intra-amniotic infection (fever or prolonged ROM)
  - bladder distension (preventing uterine contraction)

2. Tissue
- retained placental products (membranes, cotyledon, or succenturiate lobe)
- retained blood clots in an atonic uterus
- GTN
- abnormal placentation (e.g. placenta accreta)

3. Trauma
- laceration (vagina, cervix, or uterus), episiotomy, hematoma (vaginal, vulvar, or retroperitoneal), uterine rupture, and uterine inversion

4. Thrombin
- coagulopathy (pre-existing or acquired)
  - most identified prior to delivery (low platelets increases risk)
  - includes hemophilia, DIC, ITP, TTP, and VWD
  - therapeutic anticoagulation

DDx of Early PPH – 4 Ts
Tone (atony)
Tissue (retained placenta, clots)
Trauma (laceration, inversion)
Thrombin (coagulopathy)

DDx of Late PPH
Retained products
± endometritis
Sub-involution of uterus

Investigations
- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of atony, retained tissue, or trauma
- may be helpful to observe red-top tube of blood – no clot in 7-10 min indicates coagulation problem

Management
- ABCs, call for help
- 2 large bore IVs, run crystalloids wide open
- CBC, coagulation profile, fibrinogen, cross and type packed RBCs
- treat underlying cause
- Foley catheter to empty bladder and monitor urine output

Medical Therapy for Atony
- oxytocin 10 IU IM is preferred in low-risk vaginal deliveries, oxytocin IV infusion (20-40 IU in 1000 mL crystalloid at 150 mL/h) is an acceptable alternative; oxytocin 5-10 IU IV bolus (20-40 IU in 250 mL crystalloid) can be used after vaginal birth, but not with elective CD
- carbetocin, a long-acting oxytocin, 100 µg IV bolus over 1 min for elective CD or 100 µg IM for vaginal deliveries with 1 risk factor for PPH (instead of a continuous oxytocin infusion)
- methylergonovine maleate (Ergotamine®) 0.25 mg IM/slow IV q2 h up to 1.25 mg; can be given as IV bolus of 0.125 mg (contraindicated in HTN)
- carboprost (Hemabate®), a synthetic $PGF_{1\alpha}$ analog, 250 µg IM/IMM q15 min to max 2 mg (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary (asthma), renal, and hepatic dysfunction)
- misoprostol (Cytotec®) 600-800 µg PO/SL (faster) or PR/PV (side effect: pyrexia if >600 µg)
- tranexamic acid (Cyklokapron®), an antifibrinolytic, 1 g IV

Local Control for Atony
- bimanual massage: elevate the uterus and massage through patient's abdomen
- uterine packing (mesh with antibiotic treatment)
- Bakri Balloon for tamponade: may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR
- manual removal if retained placenta (can also be used to treat PPH due to other causes)

Surgical Therapy (Intractable PPH) for Atony
- D&C (beware of vigorous scraping, which can lead to Asherman's syndrome) (can also be used to treat PPH due to other causes)
- embolization of uterine artery or internal iliac artery by interventional radiologist
- laparotomy with bilateral ligation of uterine artery (may be effective), or internal iliac artery ± compression sutures (B-Lynch or Cho sutures) (can also be used to treat PPH due to trauma and early thrombus)
- hysterectomy last option, with angiographic embolization if post-hysterectomy bleeding

Retained Placenta

Definition
- placenta undelivered after 30 min postpartum

Etiology
- placenta trapped behind a partially closed cervix (trapped or incarcerated placenta)
- placenta adherent to uterine wall (placenta adherens)
- abnormal placental implantation (placenta accreta, placenta increta, and placenta percreta)

Risk Factors
- placenta previa, prior CD, post-pregnancy curettage, prior manual placental removal, and uterine infection

Clinical Features
- risk of PPH and infection

Investigations
- explore uterus
- assess degree of blood loss

Management
- 2 large bore IVs, type and screen
- Brandt maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure cephalad to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL normal saline into umbilical vein
- manual removal if above fails
- D&C if required (U/S guidance if available)
- cefazolin 2 g IV if manual removal or D&C

Uterine Inversion

Definition
- inversion of the uterus through cervix ± vaginal introitus

Etiology/Epidemiology
- often iatrogenic (excessive cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous women (lax uterine ligaments)
- 1 in 1500 to 1 in 2000 deliveries

Clinical Features
- can cause profound vasovagal response with bradycardia, vasodilation, and hypovolemic shock
- shock may be disproportionate to maternal blood loss

Management
- urgent management essential, call anesthesia
- ABCs: initiate IV crystalloids
- can use tocolytic drug (see *Preterm Labour, OB16*) or nitroglycerin IV to relax uterus and aid replacement
- replace uterus without removing placenta
- remove placenta manually and withdraw slowly
- IV oxytocin infusion (only after uterus replaced)
- re-explore uterus
- may require general anesthetic ± laparotomy

Postpartum Fever

Definition
- fever >38°C on any two of the first 10 d postpartum, except the 1st day

Etiology
- endometritis
- wound infection (check CD and episiotomy sites)
- mastitis/breast engorgement
- UTI
- atelectasis
- pneumonia
- DVT or pelvic thrombophlebitis

Etiology of Postpartum Fever

B-5W
Breast: engorgement, mastitis
Wind: atelectasis, pneumonia
Water: UTI
Wound: episiotomy, CD site infection
Walking: DVT, thrombophlebitis
Womb: endometritis

Investigations
- detailed history and physical exam, relevant cultures
- for endometritis: blood and genital cultures
- serum lactic acid for early detection of sepsis

Treatment
- depends on etiology
  - infection: empiric antibiotics, adjust when sensitivities available
- endometritis: clindamycin + gentamicin/tobramycin IV
- mastitis: cloxacillin or cephalexin
- wound infection: cephalexin + frequent sitz baths for episiotomy site infection
  - DVT: anticoagulants
- prophylaxis against post-CD endometritis: administer cefazolin 2-4 g IV (based on BMI) 30 min prior to skin incision

ENDOMETRITIS
- definition: inflammation of the endometrium most commonly due to infection
- clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling vaginal discharge, or lochia
- treatment: depends on infection severity; oral antibiotics if well, IV antibiotics with hospitalization in moderate to severe cases

Risk Factors for Endometritis
CD, intrapartum chorioamnionitis, prolonged labour, prolonged ROM, and multiple vaginal examinations

VENOUS THROMBOEMBOLISM
- see *Venous Thromboembolism, OB32*

Mastitis

- definition: inflammation of mammary glands
- must rule out inflammatory carcinoma, as indicated
- differentiate from mammary duct ectasia: mammary duct(s) beneath nipple clogged and dilated ± ductal inflammation ± nipple discharge (thick, grey to green), often postmenopausal individuals

Table 22. Lactational vs. Non-Lactational Mastitis

	Lactational	Non-Lactational
Epidemiology	More common than non-lactational Often 2-3 wk postpartum	Periductal mastitis most common Mean age 32 yr
Etiology	*S. aureus*	May be sterile May be infected with *S. aureus* or other anaerobes Smoking is risk factor May be associated with mammary duct ectasia
Symptoms	Unilateral localized pain Tenderness Erythema	Subareolar pain May have subareolar mass Discharge (variable colour) Nipple inversion
Treatment	Heat or ice packs Continued nursing/pumping Antibiotics (cloxacillin/cephalexin) (erythromycin if penicillin-allergic)	Broad-spectrum antibiotics and I&D Total duct excision (definitive)
Abscess	Fluctuant mass Purulent nipple discharge Fever, leukocytosis Discontinue nursing, IV antibiotics (nafcillin/oxacillin), I&D usually required	If mass does not resolve, fine-needle aspiration to exclude cancer and U/S to assess presence of abscess Treatment includes antibiotics, aspiration, or I&D (tends to recur) May develop mammary duct fistula A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually *S. aureus*)

Postpartum Mood Alterations

POSTPARTUM BLUES

- 40-80% of new mothers, onset 3-10 d postpartum; extension of the "normal" hormonal changes and adjustment to a new baby
- self-limited, should resolve by 2 wk
- manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness, fatigue, irritability, poor concentration/despondency, anxiety, and insomnia

POSTPARTUM DEPRESSION

- **definition**: major depression occurring in an individual within 6 mo of childbirth (see Psychiatry, PS10)
- **epidemiology**: 10-15%, risk of recurrence 50%
- **risk factors**:
  - personal or family history of depression (including PPD)
  - prenatal depression or anxiety
  - stressful life situation
  - poor support system
  - unwanted pregnancy
  - colicky or sick infant
- **clinical features**: suspect if the "blues" last beyond 2 wk, or if the symptoms in the first 2 wk are severe (e.g. extreme disinterest in the baby, suicidal or homicidal/infanticidal ideation)
- **assessment**: Edinburgh Postnatal Depression Scale or others
- **treatment**: antidepressants, psychotherapy, supportive care, and electroconvulsive therapy if refractory
- **prognosis**: interferes with bonding and attachment, may have long-term effects

POSTPARTUM PSYCHOSIS

- **definition**: acute psychotic episode triggered by the complex psychosocial stressors and hormonal changes that occur following childbirth. Symptoms usually present within the first 2 wk but can last for months
- **epidemiology**: rare (0.2%), but 50% risk of recurrence in next pregnancy if experienced in previous pregnancy. Increased risk in individuals with bipolar disorder, schizoaffective disorder, schizophrenia, or other psychotic illness, or personal or family history of postpartum psychosis
- **treatment**: psychiatric emergency as risk of infanticide. Typically requires hospitalization, mood stabilizer, and antipsychotics

Postpartum Care

Postpartum Office Visit at 6 Weeks

Care of Mother (The 10 Bs)

- **B**e careful: do not use douches or tampons for 4-6 wk post-delivery
- **B**e fit: encourage gradual increases in walking, Kegel exercises
- **B**irth control: assess for use of contraceptives
- **B**reastfeeding is not as effective as other methods of birth control (see Gynecology, GY15, for more detail about different contraceptive options postpartum)
  - lactational amenorrhea approved by WHO for up to 6 mo if meets criteria: 1) amenorrhea; 2) fully or nearly fully breastfeeding (no interval of >4-6 h between breastfeeds); and 3) <6 mo postpartum
- **B**ladder: assess for urinary incontinence, maintain high fluid intake
- **B**lood pressure: especially if gestational HTN
- **B**lood tests: CBC (for anemia if had PPH, TSH if subclinical hypothyroidism in pregnancy, 75 g OGTT if GDM)
- **B**lues: (see *Postpartum Mood Alterations, OB49*)
- **B**owel: fluids and high-fibre foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain meds, doughnut cushion, sitz baths, and ice compresses
- **B**reast and pelvic exam: watch for Staphylococcal or Streptococcal mastitis/abscess, ± Pap smear at 6 wk if due for screening

Physiological Changes Postpartum

- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains firmness
  - should involute ~1 cm below umbilicus per day in first 4-5 d, reaches non-pregnant state in 4-6 wk postpartum
- ovulation resumes in ~45 d after giving birth, non-lactating patients usually ovulate sooner than lactating patients
- lochia: normal vaginal discharge postpartum, uterine decidual tissue sloughing
  - decreases and changes in colour from red (lochia rubra; presence of erythrocytes, 3-4 d) → pale (lochia serosa) → white/yellow (lochia alba; residual leukorrhea) over 3-6 wk
- foul-smelling lochia suggests endometritis

Breastfeeding Problems

- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisturizer, topical steroid if needed
- mastitis: treat promptly (see *Postpartum Pyrexia, OB48*)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see *Table 23*)

Bladder Dysfunction

- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management for stress and urge incontinence: pelvic floor retraining with Kegel exercises/pelvic physiotherapy, vaginal cones or pessaries, and lifestyle modifications (e.g. limit fluid, caffeine intake, local vaginal estrogen in breastfeeding patients to strengthen vaginal mucosa)

Puerperal Pain

- "after pains" common in first 3 d due to uterine contractions; encourage simple analgesia
- ice packs and sitz baths can be used on perineum if painful
- encourage regular analgesia and stool softener

The acronym "**BUBBLES**" for what to ask about when rounding on postpartum care. Modify this for CD or vaginal delivery

Baby care and breastfeeding– Latch? Amount?
Uterus – Firm or boggy?
Bladder function – Voiding well? Dysuria?
Bowel function – Passing gas or stool? Constipated?
Lochia or discharge – Any blood?
Episiotomy/laceration/incision – Pain controlled?
Symptoms of VTE – Dyspnea? Calf pain?

Breastfeeding and Drugs

Table 23. Drug Safety During Breastfeeding

Safe During Breastfeeding	Contraindicated When Breastfeeding
Analgesics (e.g. acetaminophen, NSAIDs)	Chloramphenicol (bone marrow suppression)
Anticoagulants (e.g. heparin)	Cyclophosphamide (immune system suppression)
Antidepressants (e.g. sertraline, fluoxetine, tricyclic antidepressants)	Sulphonamides (in G6PD deficiency, can lead to hemolysis)
Antiepileptics (e.g. phenytoin, carbamazepine, valproic acid)	Nitrofurantoin (in G6PD deficiency, can lead to hemolysis)
Antihistamines	Tetracycline
Antimicrobials (e.g. penicillins, aminoglycosides, cephalosporins)	Lithium
β-adrenergics (e.g. prorpanolol, labetalol)	Phenindione
Insulin	Bromocriptine
Steroids	Antineoplastics and immunosuppressants
OCP (low dose) – although estrogen-containing OCPs may decrease breast milk production	Psychotropic drugs (relative contraindication)

Common Medications

Table 24. Common Medications

Drug Name (Brand Name)	Dosing Schedule	Indications/Comments
betamethasone valerate (Celestone®)	12 mg IM q24 h x 2 doses	Enhancement of fetal pulmonary maturity for PTL
carboprost (Hemabate®)	0.25 mg IM/IMM q15 min Max 2 mg	Treatment of uterine atony
cefazolin	2 g IV then 1 g q8 h	GBS prophylaxis (penicillin allergic and not at risk for anaphylaxis)
clindamycin	900 mg IV q8 h	Used in endometritis
dexamethasone	6 mg IM q12 h x 4 doses	Enhancement of fetal pulmonary maturity for PTL
dinoprostone (Cervidil®: PGE_2 impregnated thread)	10 mg PV (remove after 12 h) Max 3 doses	Induction of labour Advantage: can remove if tachysystole
doxylamine succinate (Diclectin®)	2 tablets qhs + 1 tablet qam + 1 tablet qpm Max 8 tablets/d	Each tablet contains 10 mg doxylamine succinate with vitamin B_6 Used first-line for N/V in pregnancy, including hyperemesis gravidarum
erythromycin	250 mg PO q6 h x 10 d	To prolong pregnancy and decrease maternal and neonatal morbidity for patients who are not in labour in PPROM
folic acid	0.4-1 mg PO once daily x 1-3 mo preconception and T1 4 mg PO once daily with past Hx of NTD/high risk for NTD	Prevention of ONTD
methylergonovine maleate (Ergotamine®)	0.25 mg IM/slow IV q2 h up to 1.25 mg or IV bolus 0.125 mg	Treatment of uterine atony
misoprostol (Cytotec®)	600-1000 µg PR x 1 dose 400 µg PO/SL x 1 dose or 800 µg PV x 1 dose 3-7 d after methotrexate	For treatment of PPH For medical abortion/retained products of conception
oxytocin (Pitocin®)	0.5-2.0 mU/min IV or 10 IU/L normal saline increase by 1-2 mU/min q20-60 min 10 IU IM at delivery of anterior shoulder (or after delivery of placenta) 20 IU/L normal saline or Ringer's Lactate IV continuous infusion	Induction/augmentation of labour Prevention of uterine atony Treatment of uterine atony
penicillin G	5 million IU IV, then 2.5 million IU IV q4 h until delivery	GBS prophylaxis
PGE_2gel (Prostin® gel)	0.5 mg PV q6-12 h; Max 3 doses	Induction of labour
Rh IgG (RhoGAM®)	300 µg IM x 1 dose	Given to Rh-negative women Routinely at 28 wk GA Within 72 h of birth of Rh+ fetus Positive Kleihauer-Betke test With any invasive procedure in pregnancy Ectopic pregnancy Antepartum hemorrhage and first trimester bleeding Miscarriage or therapeutic abortion (dose: 50 µg IM only)

Landmark Obstetrics Trials

Trial Name	Reference	Clinical Trial Details
PRETERM LABOUR		
Meis Trial	NEJM 2003; 348:2379-2385	**Title**: Prevention of Recurrent Preterm Delivery by 17 α-Hydroxyprogesterone Caproate **Purpose**: Confirm the results of several small trials that have suggested that the use of α-hydroxyprogesterone caproate (17P) may reduce the risk of recurrent preterm delivery. **Methods**: Double-blind placebo-controlled trial involved pregnant women with a history of spontaneous preterm delivery. Women received weekly injections of either 250 mg 17P or an inert placebo until delivery or 36 wk GA. **Results**: Treatment with 17P significantly reduced the risk of delivery at <37 wk (36.3% vs. 54.9%), <35 wk (20.6% vs. 30.7%), and <32 wk (11.4% vs. 19.6%). Infants of women treated with 17P had lower rates of enterocolitis, hemorrhage, and need for supplemental oxygen. **Conclusion**: Weekly injections of 17P resulted in substantial reductions in the rate of recurrent preterm delivery among women and reduced the likelihood of several complications in the infants.
MULTI-FETAL GESTATION		
Twin Birth Study	NEJM 2013; 369:1295-1305	**Title**: A Randomized Trial of Planned Cesarean or Vaginal Delivery for Twin Pregnancy **Purpose**: Twin births are associated with a higher risk of adverse perinatal outcomes. It is unclear whether CD results in lower risk of negative outcomes than vaginal delivery in twin pregnancies. **Methods**: Women between 32-38+6 GA with a twin pregnancy and with the first twin in the cephalic position were randomly assigned to planned CD or planned vaginal delivery. **Results**: There was no significant difference in the outcomes between the planned CD and the planned vaginal delivery group (2.2% and 1.9%, respectively; odds ratio with planned CD 1.16; 95% confidence interval, 0.77 to 1.74; P=0.49). **Conclusion**: There was no benefit from planned CD compared with planned vaginal delivery of twins between 32 and 38 wk GA if the first twin was in the cephalic position.

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OP Ophthalmology

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Acronyms

AION	anterior ischemic optic neuropathy	EBV	Epstein-Barr virus	LASIK	laser-assisted in situ keratomileusis	RA	rheumatoid arthritis
AMD	age-related macular degeneration	EOM	extraocular movement	MS	multiple sclerosis	RAPD	relative afferent pupillary defect
BCVA	best-corrected visual acuity	FML	fluorometholone	OCT	optical coherence tomography	RD	retinal detachment
BRAO	branch retinal artery occlusion	GAT	Goldmann applanation tonometry	OHT	ocular hypertension	ROP	retinopathy of prematurity
BRVO	branch retinal vein occlusion	GCA	giant cell arteritis	PACG	primary angle-closure glaucoma	RPE	retinal pigment epithelium
CDR	cup-to-disc ratio	GPA	granulomatosis with polyangiitis	PDR	proliferative diabetic retinopathy	SMILE	small incision lenticule extraction
CMV	cytomegalovirus	GPC	giant papillary conjunctivitis	PDT	photodynamic therapy	SPK	superficial punctate keratitis
CRAO	central retinal artery occlusion	HRT	Heidelberg retinal tomography	PERRLA	pupils equal, round, and reactive to light and accommodation	TED	thyroid eye disease
CRVO	central retinal vein occlusion	INO	internuclear ophthalmoplegia	POAG	primary open-angle glaucoma	TIA	transient ischemic attack
D	diopter	IOL	intraocular lens	PRK	photorefractive keratectomy	VA	visual acuity
DR	diabetic retinopathy	IOP	intraocular pressure	PVD	posterior vitreous detachment	VEGF	vascular endothelial growth factor
						YAG	yttrium aluminum garnet

Basic Anatomy Review

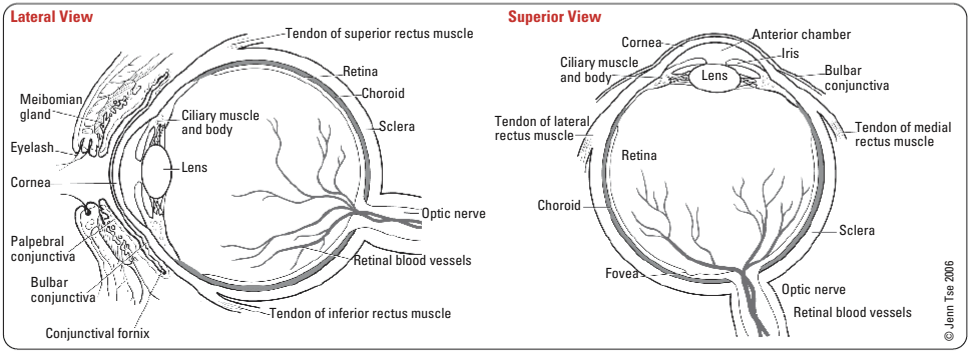


Figure 1. Anatomy of the eye

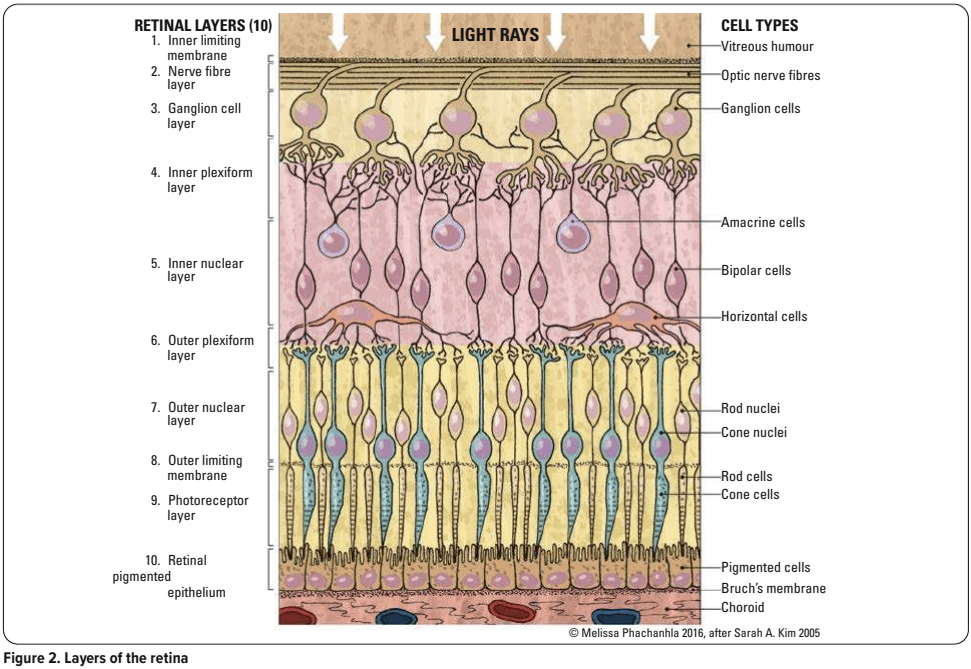


Figure 2. Layers of the retina

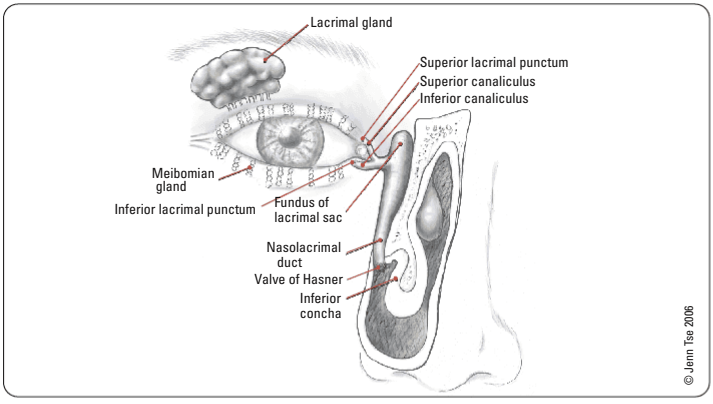


Figure 3. Tear drainage from the eye (lacrimal apparatus)

Differential Diagnoses of Common Presentations

Loss of Vision

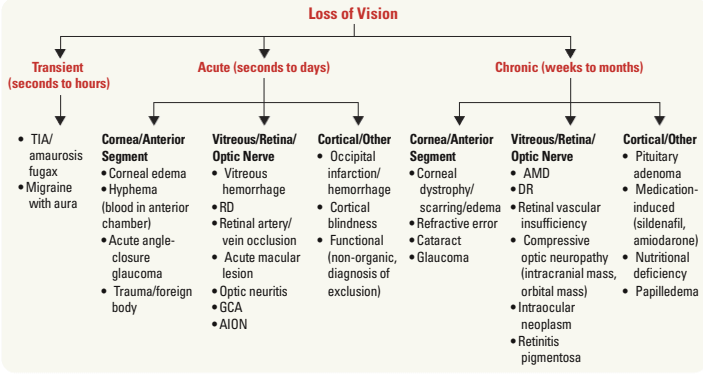


Figure 4. Loss of vision

Red Eye

Table 1. Common Causes of Red Eye

Common Causes		
Lids/Orbit/Lacrimal System	**Cornea**	**Other**
Hordeolum/chalazion	Foreign body (including contact lens)	Trauma
Blepharitis	Keratitis	Postoperative endophthalmitis
Entropion/ectropion	Abrasion, laceration	Pharmacologic (e.g. prostaglandin analogues)
Foreign body/laceration	Ulcer	
Dacryocystitis/dacryoadenitis		
Conjunctiva/Sclera	**Anterior chamber**	
Subconjunctival hemorrhage	Anterior uveitis (iritis, iridocyclitis)	
Conjunctivitis	Acute glaucoma	
Dry eyes	Hyphema (blood in anterior chamber)	
Pterygium	Hypopyon (pus in anterior chamber)	
Episcleritis/scleritis		
Preseptal/orbital cellulitis		

Table 2. Common Differential Diagnoses of Red Eye

	Conjunctivitis	Acute Iritis	Acute Glaucoma	Keratitis (Corneal Ulcer)
Discharge	Bacterial: purulent Viral: serous/mucoid Allergic: mucoid	No	Clear	Bacterial: ± purulent
Pain	±	++ (dull/achy)	+++ (nausea)	++ (sharp)
Photophobia	No	+++	+	++
Blurred Vision	No	++	+++	Varies
Pupil	Normal	Smaller	Fixed in mid-dilation	Same or smaller
Injection	Diffuse conjunctival injection involving the bulbar conjunctiva for 360° + palpebral or tarsal conjunctiva	Ciliary flush (peri-limbal)	Conjunctival injection	Possible conjunctival injection
Cornea	Normal (subepithelial infiltrates in adenoviral conjunctivitis)	Keratic precipitates	Cloudy	Infiltrate, edema, and may have keratic precipitates
IOP	Normal	Varies	Increased markedly	Normal or slightly decreased
Anterior Chamber	Normal	+++ Cells and flare	Shallow	Cells and flare or normal, and may have hypopyon
Nausea and Vomiting	No	No	+++	No
Other	Large, tender pre-auricular node(s) if viral	Posterior synechiae	Coloured haloes	

Ocular Pain

- differentiate from eye fatigue (asthenopia)
- ocular surface disease (dry eye)
- herpes zoster prodrome
- trauma/foreign body
- blepharitis
- keratitis corneal abrasion/ulcer
- acute glaucoma
- anterior uveitis
- scleritis
- episcleritis
- optic neuritis

Floaters

- PVD (often secondary to age-related vitreous syneresis)
- vitreous hemorrhage
- retinal tear/detachment
- intermediate uveitis (pars planitis)
- posterior uveitis (chorioretinitis)

Flashes of Light (Photopsia)

- PVD (often secondary to age-related vitreous syneresis)
- retinal tear/detachment
- migrainous visual aura

Photophobia (Severe Light Sensitivity)

- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis meningitis/encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

Diplopia (Double Vision)

Table 3. Common Causes of Diplopia

Binocular Diplopia	Monocular Diplopia
Definition	
Occurs with both eyes open, eliminated with occlusion of either eye	Occurs with one eye open, remains with occlusion of unaffected eye
Causes	
Decompensated congenital strabismus	Optical factors: refractive error/astigmatism
Ocular motor nerve dysfunction: III, IV, VI nerve palsy	Mechanical process: dislocated lens, postoperative sequelae (cataract surgery, peripheral laser iridotomy)
Neuromuscular junction disease: myasthenia gravis, botulism	Other: strands of mucus in tear film, keratoconus
Mechanical process: muscle restriction/entrapment, TED	
Supranuclear causes: skew deviation, dorsal midbrain syndrome	

Ocular Problems in the Contact Lens Wearer

- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- GPC/contact lens allergy
- SPK from dry eyes
- limbal stem cell deficiency
- corneal neovascularization
- sterile corneal infiltrates (immunologic)
- infected ulcers (*Pseudomonas, Acanthamoeba*)

Ocular Emergencies

These require urgent ophthalmology consultation for management

Sight-Threatening

- lid laceration
- globe rupture
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute glaucoma
- CRAO
- intraocular foreign body
- RD)
- endophthalmitis
- GCA

Life-Threatening

- proptosis (rule out cavernous sinus fistula or thrombosis)
- cranial nerve (CN) III palsy with dilated pupil (rule out intracranial aneurysm or externally compressive lesion)
- papilledema (elevated or increased ICP workup)
- orbital cellulitis
- leukocoria: white pupillary reflex (absent red reflex: rule out retinoblastoma in children)

The Ocular Examination

VISUAL ACUITY

Visual Acuity – Distance

- Snellen VA = smallest line patient can read on the chart at the testing distance (usually 20 ft or 6 m)
  - e.g. 20/40 = what the patient can see at 20 feet away (numerator) is what a "normal" person can see at 40 feet away (denominator)
- distance VA should be tested with distance glasses on in order to obtain BCVA
- testing hierarchy for low vision: Snellen VA (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)

Example 1

$\overline{SC}$ V 20/40 −1
20/80 +2 → 20/25 PH

Example 2

$\overline{CC}$ V CF 3'
HM

Note: RIGHT EYE visual acuity always listed on top.

V	Vision
SC	Without correction
CC	With correction
20/40 -1	All except one letter of 20/40
20/80+2	All of 20/80 plus two letters of 20/70
PH	Visual acuity with pinhole correction
CF	Counting fingers
HM	Hand motion

Figure 5. Ophthalmology nomenclature for visual acuity

OD = oculus dexter = right eye
OS = oculus sinister = left eye
OU = oculus uterque = both eyes

Snellen VA of 20/20 equates to "normal" vision

Normal Infant and Child Visual Acuity Equivalent
6-12 mo: 20/120
1-2 yr: 20/80
2-4 yr: 20/20

- minimum visual requirements to operate a non-commercial automobile in Ontario are: 20/50 BCVA with both eyes open and examined together, 120° continuous horizontal visual field, and 15° continuous visual field above and below fixation

Visual Acuity – Near
- use pocket vision chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point Number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance VA possible (e.g. immobile patient, no distance chart available)

Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics
- newborns
  - VA cannot be tested conventionally
- 3 mo-3 yr: can usually only assess visual function, not acuity
  - test each eye for fixation symmetry using an interesting object
  - normal function noted as "CSM" = central, steady, and maintained
- 3 yr until alphabet known
  - pictures or letter cards/charts such as HOTV or Sheridan-Gardiner test (children point to optotypes on a matching card)
  - tumbling "E" chart

COLOUR VISION
- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye (usually 14 plates)
- important for testing optic nerve function and identifying an optic neuropathy (e.g. optic neuritis)
- note: red-green colour blindness is sex-linked and occurs in 7-10% of males

VISUAL FIELDS
- estimation of visual field loss: test by confrontation (4 quadrants, each eye tested separately)
- accurate, quantifiable assessment: automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- AMD monitoring: Amsler grid (each eye tested separately) to check for central or paracentral scotomas (blind spots) and distortion
- see Neurology, N15 for visual field defects

PUPILS
- use reduced room illumination with patient focusing on distant, fixed object to prevent near reflex
- examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
- test for RAPD with swinging flashlight test, check by reverse RAPD test if one pupil is non-reactive
- test pupillary constriction portion of near reflex by bringing object close to patient's nose
- "normal" pupil testing often noted as PERRLA (pupils equal, round, reactive to light and accommodation)

ANTERIOR CHAMBER DEPTH
- shine light tangentially from temporal side
- if >2/3 of nasal side of iris in shadow → shallow anterior chamber
- gonioscopy is the gold-standard for assessing anterior chamber depth

The Van Herick Method (Slit-Lamp Technique)
- shine thin-angled slit beam onto the peripheral cornea of each eye, view at a 60° angle from the beam
- estimate anterior chamber depth using the ratio of corneal slit beam thickness to the space between the posterior cornea and the iris

EXTRAOCULAR MUSCLES

Alignment
- Hirschberg corneal reflex test
  - examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  - shine light into patient's eyes from ~30 cm away
  - corneal light reflex should be at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see *Strabismus, OP37*)

Movement
- examine movement of eyeball through nine cardinal positions of gaze
- identify if there is limitation of eye movement in each position of gaze
- observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end-gaze is usually normal

Diplopia
- see Neurology, N16

Test pupils using an ophthalmoscope focused on the red reflex; this will provide a better view than using a penlight

4 Ps of Inspection
Pupil: shape, size, symmetry
Position: esotropia, exotropia, central
Ptosis
Primary nystagmus

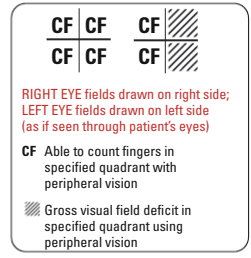

CF CF
CF CF
CF
CF
RIGHT EYE fields drawn on right side; LEFT EYE fields drawn on left side (as if seen through patient's eyes)
CF Able to count fingers in specified quadrant with peripheral vision
Gross visual field deficit in specified quadrant using peripheral vision

Figure 6. Ophthalmology nomenclature for visual fields by confrontation

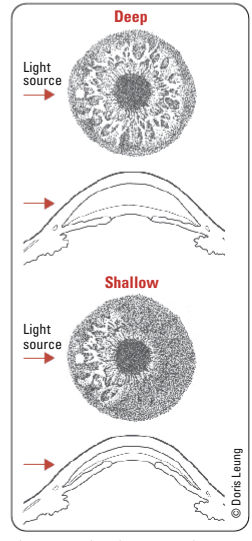


Figure 7. Estimation of anterior chamber depth

SLIT-LAMP EXAMINATION

Ocular Adnexa
- lids, lashes, and lacrimal system

Anterior Segment
- conjunctiva/sclera
- cornea
  - fluorescein dye: stains de-epithelialized cornea; dye appears fluorescent green with cobalt blue filtered light
  - Rose Bengal dye: stains devitalized corneal epithelium; dye appears red
- anterior chamber (cells, flare) and angle (Van Herick method)
- iris/pupil
- lens (assess for cataract)
- anterior vitreous

Posterior Segment (requires 78 D or 90 D lens)
- vitreous
- optic disc (colour, CDR ratio, sharpness of disc margin)
- macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
- retinal vessels
- retinal background

TONOMETRY
- measurement of IOP
- normal range is 9-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by:
  - GAT: clinical gold standard, performed using the slit-lamp with prism tip
  - Tono-Pen®: benefits are portability and use of disposable probe tips; use when GAT is inaccurate, such as when the cornea is scarred or asymmetric
  - iCare®: uses a disposable light-weight probe that contacts the cornea briefly, without anesthetic required; used especially in pediatrics
  - non-contact tonometer (NCT): air puff, least reliable
- use topical anesthetic for GAT and Tono-Pen®; apply fluorescein dye and use cobalt blue light for GAT

DIRECT FUNDOSCOPY
- best performed with pupils dilated (for list of mydriatic and cycloplegic drugs see *Table 13, OP44*)
  1. assess red reflex
     - light reflected off the retina produces a "red reflex" when viewed from ~1 foot away
     - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract)
     - white reflex indicates leukocoria, see *Leukocoria, OP40*
  2. examine the posterior segment of the eye
     - vitreous
     - optic disc (colour, CDR, sharpness of disc margin)
     - macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
     - retinal vessels
     - retinal background
- contraindications to pupillary dilatation
  - shallow anterior chamber – can precipitate acute angle-closure glaucoma
  - iris-supported anterior chamber lens implant
  - potential neurologic abnormality requiring pupil evaluation
  - use caution with cardiovascular disease – mydriatics may cause tachycardia and HTN

Optics

REFRACTION
- two techniques used
  - cycloplegic refraction: use of streak retinoscope and lenses to objectively determine the refraction under temporary paralysis of accommodation (with cyclopleges)
  - manifest refraction: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
- a typical lens prescription would contain:
  - sphere power in dioptres (measurement of refractive power of lens, equal to reciprocal of focal length in metres)
  - cylinder power in dioptres to correct astigmatism
  - axis of cylinder in degrees
  - "add" (bifocal/progressive reading lens) for presbyopes
  - e.g. -1.50 + 1.00 x 120°, add +2.00

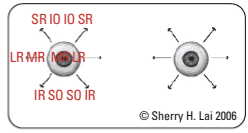


Figure 8. Diagnostic positions of gaze for isolated primary actions of extraocular muscles

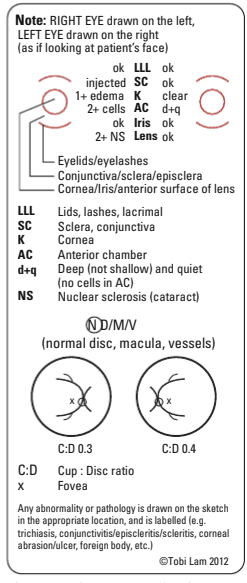

Note: RIGHT EYE drawn on the left, LEFT EYE drawn on the right (as if looking at patient's face)
ok LLL ok
injected SC ok
1+ edema K clear
2+ cells AC d+q
ok Iris ok
2+ NS Lens ok
Eyelids/eyelashes
Conjunctiva/sclera/episclera
Cornea/Iris/anterior surface of lens
LLL Lids, lashes, lacrimal
SC Sclera, conjunctiva
K Cornea
AC Anterior chamber
d+q Deep (not shallow) and quiet (no cells in AC)
NS Nuclear sclerosis (cataract)
N D/M/V
(normal disc, macula, vessels)
C:D 0.3
C:D 0.4
C:D Cup : Disc ratio
x Fovea
Any abnormality or pathology is drawn on the sketch in the appropriate location, and is labelled (e.g. trichiasis, conjunctivitis/episcleritis/scleritis, corneal abrasion/ulcer, foreign body, etc.)
©Tobi Lam 2012

Figure 9. Slit-lamp examination note

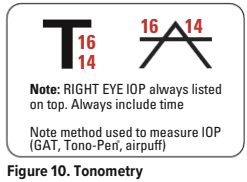

T 16 14
16 14
Note: RIGHT EYE IOP always listed on top. Always include time
Note method used to measure IOP (GAT, Tono-Pen, airpuff)

Figure 10. Tonometry

Extraocular Muscle Innervations

LR6 SO4 AE3
Lateral **R**ectus via CN **VI**
Superior **O**blique via CN **IV**
All **E**lse via CN **III** (superior, medial, and inferior rectus, inferior oblique)

Aqueous Flare

Resembles "headlights in fog" (Tyndall effect) in a beam of light

Results from increased aqueous turbidity secondary to protein leaking from blood vessels

Distinguish from aqueous cells (individual cells in anterior chamber)

LASER REFRACTIVE EYE SURGERY

- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK, LASIK, and SMILE
- potential risks/side effects: infection, under/overcorrection, increased glare/halo perception at night, corneal haze (PRK only), dry eyes (more common in LASIK than PRK), regression, and corneal ectasia
- LASIK-specific: flap complications such as free cap (loss of flap), traumatic flap dislocations, buttonhole flap, and epithelial ingrowth)

Table 4. Optics

	Pathophysiology	Clinical Features	Treatment	Complications
Emmetropia	Image of distant objects focuses directly on the retina	No refractive error		
Myopia	Globe too long relative to refractive mechanisms, or refractive mechanisms too strong	"Nearsightedness" Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with DM-induced cataracts Blurring of distance vision; near vision usually unaffected Prevalence: 30-40% in U.S. population; higher among Asians	Correct with negative diopter/concave/"negative" lenses to diverge light rays Refractive eye surgery	Retinal tear/detachment, chorioretinal atrophy, myopic maculoschisis leading to formation of macular hole, open-angle glaucoma
Hyperopia	Globe too short relative to refractive mechanisms, or refractive mechanisms too weak May be developmental or due to any etiology that shortens globe	"Farsightedness" Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia and amblyopia if not corrected (see *Strabismus, OP37*) 30s-40s: blurring of near vision due to decreased accommodation, may need reading glasses >50s: blurring of distance vision due to severely decreased accommodation	When symptomatic, correct with positive diopter/convex/"plus" lenses to converge light rays Refractive eye surgery	Angle-closure glaucoma, particularly later in life as lens enlarges
Astigmatism	Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped) **Two types** Regular – curvature uniformly different in meridians at right angles to each other Irregular – distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye	Affects ~30% of population, with prevalence increasing with age Mild astigmatism unnoticeable Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches	Correct with cylindrical lens (if regular) Consider contact lens (if irregular) Refractive eye surgery	
Presbyopia	Normal aging process (>40 yr) Hardening/reduced deformability of lens results in decreased accommodative ability Accommodative power is 14D at age 10, diminishes to 3.5D by age 40 Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia)	If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected If initially myopic, person removes distance glasses to read If initially hyperopic, symptoms of presbyopia occur earlier	Correct with positive diopter/convex/"plus" lenses for reading	
Anisometropia	Difference in refractive errors between eyes			Second most common cause of amblyopia in children

Central Corneal Thickness (CCT)
Average CCT = 550 µm
By GAT, IOP is over-estimated with thick corneas and under-estimated with thin corneas

Structures Responsible for Refractive Power
Cornea (2/3)
Lens (1/3)

Myopia

LMN
Long globe
Myopic
Negative correction/Nearsighted

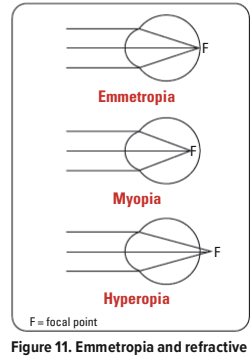


Figure 11. Emmetropia and refractive errors

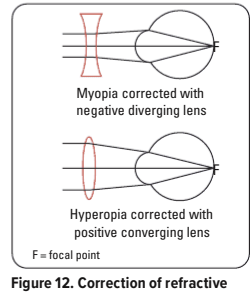


Figure 12. Correction of refractive errors

The Orbit

Globe Displacement

Table 5. Exophthalmos (Proptosis) and Enophthalmos

	Exophthalmos (Proptosis)	Enophthalmos
Definition	Anterior displacement (protrusion) of the globe Exophthalmos generally refers to an endocrine etiology or protrusion of >18 mm (as measured by a Hertel exophthalmometer) Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of <18 mm Difference of >2mm asymmetry in protrusion of patient's eye is considered abnormal	Posterior displacement (retraction) of the globe
Investigations	CT/MRI head/orbits, ultrasound orbits, thyroid function tests	CT/MRI orbits
Etiology	Note: rule out pseudoexophthalmos (e.g. lid retraction) Graves' disease (unilateral or bilateral, most common cause in adults) Orbital cellulitis (unilateral, most common cause in children) 1° or 2° orbital tumour Orbital/retrobulbar hemorrhage Cavernous sinus thrombosis or fistula	"Blow-out" fracture (see *Ocular Trauma, OP41*) Orbital fat atrophy Congenital abnormality Metastatic disease (e.g. breast cancer)

Preseptal Cellulitis

Definition
- infection of soft tissue anterior to orbital septum

Etiology
- usually follows periorbital trauma or dermal infection
- sinusitis is the main risk factor in children

Clinical Features (see Table 6, OP10)

Treatment
- systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
- children: systemic Abx (Cephalexin, ampicillin, amoxicillin-clavulanic acid) & nasal decongestants (oxymetazoline nasal spray) to promote spontaneous drainage of infected sinus
- teenagers/adults: oral antibiotics (ampicillin-sulbactam, septra DS, clindamycin) + warm compresses
- intravenous antibiotics (e.g. Ceftriaxone + Vancomycin) if: a) children <5 years of age, b) severe, c) failed oral antibiotics
- community associated-MRSA – susceptible to septra DS, rifampin, clindamycin
- hospital-MRSA – often only susceptible to vancomycin, linezolid

Orbital Cellulitis

Definition
- OCULAR and MEDICAL EMERGENCY
- inflammation of orbital contents posterior to orbital septum
- common in children, elderly, and immunocompromised

Etiology
- usually secondary to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

Clinical Features (see Table 6, OP10)
- the diagnosis of orbital cellulitis is based on clinical examination
- for equivocal findings, difficult examinations, or presence of nasal discharge, perform CT or MRI orbits and sinuses

Treatment
- admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
- may require surgical drainage of abscess with close follow-up, especially in children

Complications
- optic nerve inflammation, cavernous sinus thrombosis, meningitis, brain abscess with possible loss of vision, and death

Role of Oral Corticosteroids in Orbital Cellulitis
Am J Ophthalmol 2013;156:178-183
Purpose: To evaluate the role of oral corticosteroids as an anti-inflammatory adjunct for the treatment of orbital cellulitis.
Methods: RCT of 21 patients with acute onset (within 14 d) of orbital cellulitis with or without abscess. There were 7 patients in group 1 (standard IV antibiotics) and 14 in group 2 (adjuvant steroids).
Results: Patients in group 2 showed earlier resolution of periorbital edema, conjunctival chemosis, pain, proptosis, and EOM deficits, including decreased duration of IV antibiotics and hospital stay ($P<0.05$ for all).
Conclusion: The use of oral steroids as an adjunct to IV antibiotics for orbital cellulitis may decrease inflammatory symptoms with a low-risk of worsening infection.

Table 6. Clinical Features of Preseptal and Orbital Cellulitis

Finding	Preseptal Cellulitis	Orbital Cellulitis
Fever	May be present	Present
Lid Edema	Moderate to severe	Severe
Conjunctival Injection	Absent	Present
Chemosis	Absent or mild	Marked
Proptosis	Absent	Present
Pain on Eye Movement	Absent	Present
Ocular Mobility	Normal	Decreased
Vision	Normal	Diminished ± diplopia
RAPD	Absent	May be seen if severe
Leukocytosis	Moderate	Marked
Complications	Uncommon unless secondary orbital spread occurs or MRSA	Subperiosteal abscess, cranial neuropathies, cavernous sinus thrombosis, intracranial extension
Erythrocyte Sedimentation Rate (ESR)	Normal or elevated	Elevated
Additional Findings	Skin infection	Sinusitis, dental abscess

Lacrimal Apparatus

- tear film made up of three layers
  - outer oily layer (reduces evaporation): secreted by the meibomian glands
  - middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  - inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
- tears drain from the eyes through the upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrimal duct → nasal cavity behind inferior concha (see *Figure 3, OP3*)

Dry Eye Syndrome (Keratoconjunctivitis Sicca)

Definition and Etiology

- aqueous-deficient
  - Sjögren syndrome (autoimmune etiology; e.g. RA, SLE)
  - non-Sjögren syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy, anticholinergics, antihistamines, diuretics, β-blockers)
- evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  - meibomian gland dysfunction (posterior blepharitis)
  - vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  - eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  - topical ocular medications with preservatives
  - contact lenses, allergic conjunctivitis
- mixed etiologies are common

Clinical Features

- dry eyes, red eyes, foreign body sensation, eye pain, blurred vision, tearing
- slit-lamp exam: decreased tear meniscus, decreased tear break-up time (normally should be >10 s), punctate staining of cornea with fluorescein
- in severe cases, there can be filaments (strands of epithelium cells attached to corneal epithelium), corneal keratinization

Investigations

- surface damage observed with fluorescein/Rose Bengal staining
- fluorescence stains disruption of epithelial intercellular junction
- Rose Bengal stains devitalized cells and mucous strands
- decreased wetting distance in Schirmer's test

Long-term use of artificial tears with preservatives should be avoided when treating dry eyes

Complications

- erosions and scarring of cornea

Treatment

- medical: preservative-free artificial tears up to q1 h and ointment at bedtime (preservative toxicity becomes significant if used more than 4-6 x/d), short course of mild topical corticosteroids, omega-3 fatty acids orally (controversial), and eyelid hygiene for blepharitis
  - for moderate cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) or lifitegrast 5% (Xiidra®) can be used

- procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (partial surgical fusion of the lids) if severe
- treat underlying cause

Epiphora (Excessive Tearing)

Excessive tearing can be caused by dry eyes – if the tear quality is insufficient, "reflex tearing" may occur

Etiology
- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, dacryoadenitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex ("crocodile tears")

Investigations
- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

Treatment
- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation (dilation and irrigation)
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy – forming a new connection between the lacrimal sac and the nasal cavity

Dacryocystitis

Etiology
- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- gram-positive bacteria (*S. aureus, S. pneumoniae*): most common cause of acute dacryocystitis
- gram-negative bacteria (e.g. Pseudomonas species) in immunocompromised patients

Clinical Features
- pain, swelling, and redness over lacrimal sac below the medial canthus
- epiphora, crusting, ± fever
- digital pressure on the lacrimal sac may express pus through the punctum
- in the chronic form, epiphora may be the only symptom

Treatment
- warm compresses, nasal decongestants, systemic antibiotics (cephalexin if afebrile; cefazolin if febrile)
- topical antibiotics have limited value as they do not penetrate the site of infection sufficiently
- I&D; if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy

Dacryoadenitis

Etiology
- most commonly seen in children and young adults
- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: *S. aureus*, mumps, EBV, herpes zoster, *N. gonorrhoeae*
- chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, TED

Clinical Features
- pain, swelling, tearing, discharge, and redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

Treatment
- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder

Lids and Lashes

Lid Swelling

Etiology
- commonly due to allergy, which rarely leads to blepharochalasis (thinning of skin due to recurrent edema)
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatochalasis (loose skin due to aging or heredity)
- lid cellulitis, TED, trauma, and chemosis

Ptosis

Definition
- drooping of upper eyelid

Etiology
- aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
  - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- mechanical
  - incomplete opening of eyelid due to mass or scarring
- neuromuscular
  - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  - CN III palsy
  - Horner's syndrome (see *Constricted Pupil (Miosis): Horner's Syndrome, OP31*)
- congenital
- pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)
- drugs (e.g. high dose opioids, heroin abuse, pregabalin)

Treatment
- surgery (e.g. blepharoplasty, levator resection, Müller's muscle resection, and frontalis sling)
- blepharoplasty
- mild ptosis (<2 mm) with normal levator function: Muller-conjuncitval resection (Putterman) or tarso-muller-conjunctival resection
- >2 mm ptosis with normal levator function: levator advancement
- >2 mm with moderate levator function (4-10 mm of levator function): levator resection
- >2 mm with severe levator function (<4 mm of levator function): frontalis suspension
- materials for frontalis suspension: fascia lata (humor donor, or autologous but need to wait until child is 3 years or older), synthetic materials such as silicone

Trichiasis

Definition
- eyelashes are misdirected towards the ocular surface with normal lid margin position

Etiology
- may result from involutional age change, chronic inflammatory lid diseases (e.g. blepharitis), trauma, burns, Stevens-Johnson Syndrome, infection (e.g. trachoma)

Clinical Features
- patient complains of red eye, foreign body sensation, significant discomfort, tearing
- may cause corneal abrasions with secondary ulceration and scarring

Treatment
- topical lubrication, repeat eyelash epilation, electrolysis, cryotherapy, and surgical rotation of eyelid margin

Testing for Entropion
Forced lid closure: Ask patient to tighten lid then open. In entropion, lid margin rolls inwards

Entropion

Definition
- lid margin turns inward towards globe

Etiology
- involutional (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital
- rule out pseudo-entropion: trichiasis, distichiasis, epiblepharon

Clinical Features
- tearing, foreign body sensation, and red eye
- most commonly affects lower lid
- may cause corneal abrasions with secondary corneal scarring

Treatment
- lubricants, evert lid with tape, and surgery

Ectropion

Definition
- lid margin folds outward from globe

Etiology
- involutional (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, and surgery)
- mechanical (lid edema, tumour, and herniated fat)
- congenital such as ichthyosis

Testing for Ectropion
Snapback test: Pull eyelid inferiorly. In ectropion, lid remains away from globe

Clinical Features
- tearing and possibly exposure keratitis

Treatment
- topical lubrication, eyelid taping overnight, and surgery

Hordeolum (Stye)

Definition
- acute inflammation of eyelid gland: either meibomian glands (internal lid), glands of Zeis (modified sweat gland), or Moll glands (modified sebaceous gland in external lid)

Clinical Features
- infectious agent is usually *S. aureus*
- painful, red swelling of lid

Treatment
- warm compresses, lid scrubbing, gentle massage
- topical antibiotics are typically ineffective
- usually resolves within a few weeks but can persist for months, and may require I&D

Chalazion

Definition
- chronic granulomatous inflammation of a meibomian gland often preceded by an internal hordeolum

Clinical Features
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell carcinoma, meibomian gland carcinoma

Treatment
- warm compresses, lid scrubbing, gentle massage
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy

Blepharitis

Definition
- inflammation of lid margins

Etiology
- anterior blepharitis
  - Staphylococcus (*S. aureus*): ulcerative, dry scales
  - seborrheic: no ulcers, greasy scales
- posterior blepharitis
  - meibomian gland dysfunction

Clinical Features
- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids ("toothpaste sign")

Complications
- recurrent hordeola
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

Treatment
- warm compresses, lid massages, and lid washing using commercially available eyelid scrub solution
- topical or systemic antibiotics (doxycycline) as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids, omega-3 fatty acids

Xanthelasma

Definition
- eyelid xanthoma (lipid deposits in dermis of lids)

Clinical Features and Associations
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (~50% of patients)
- common in the elderly, more concerning in young people

Treatment
- excision for cosmesis only, commonly recurs

Conjunctiva

- thin, vascular mucous membrane
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

Pinguecula

Definition
- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea

Clinical Features
- associated with sun and wind exposure, aging
- benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits

Treatment
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops

Pterygium

Definition
- fibrovascular, triangular, wing-like encroachment of epithelial tissue onto the cornea

Clinical Features
- may induce astigmatism, decrease vision

Treatment
- excision for chronic inflammation, threat to visual axis, and/or cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after bare excision, lower recurrence with conjunctival autograft (~5%)

Subconjunctival Hemorrhage

- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, HTN, anticoagulation
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- 360° involvement should be highly suspicious for globe rupture if trauma history
- if recurrent, consider medical/hematologic workup, especially if non-traumatic in nature

Conjunctivitis

Etiology
- infectious
  - bacterial, viral, chlamydial, gonococcal, fungal, and parasitic
- non-infectious
  - allergic, atopic, seasonal, GPC (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
  - secondary to another disorder: dacryocystitis, dacryoadenitis, cellulitis, and systemic inflammatory disease

Types of Discharge
Allergic: mucoid
Viral: watery
Bacterial: purulent
Chlamydial: mucopurulent

Clinical Features
- red eye (conjunctival injection), chemosis
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, and lid edema
- ± preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva, overlain by vessels
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)

Follicles are usually seen in viral and chlamydial conjunctivitis
Papillae are usually seen in allergic and bacterial conjunctivitis

ALLERGIC CONJUNCTIVITIS
- associated with rhinitis, asthma, dermatitis, and hay fever
- ocular pruritus, small papillae, chemosis, redness, thickened and erythematous lids
- seasonal (pollen, grasses, plant allergens)

Treatment
- allergen avoidance, cool compresses, non-preserved artificial tears, topical or oral antihistamine, topical mast cell stabilizer (e.g. cromolyn, ketotifen, olopatadine), and topical corticosteroids

Antibiotics vs. Placebo for Acute Bacterial Conjunctivitis
Cochrane DB Syst Rev 2012;9:CD001211
Purpose: To assess the benefits and harms of antibiotic therapy in the management of acute bacterial conjunctivitis.
Criteria: RCTs with any form of antibiotic treatment compared with placebo including topical, systemic, or combined (e.g. antibiotics and steroids) antibiotic treatments.
Results: 11 RCTs, 3673 participants. Topical antibiotics improve early (2-5 d) clinical and microbiological remission rates (RR 1.36, 95% CI 1.15-1.61; RR 1.55; 95% CI 1.37-1.76) and benefit clinical remission and microbiological cure rates at a late time point (6-10 d) (RR 1.21, 95% CI 1.10-1.33; RR 1.37, 95% CI 1.24-1.52). By 6-10 d 41% of cases had resolved in the placebo group. No serious outcomes were reported in any group.
Conclusion: The use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission in comparison to placebo. Antibiotic eye drops should therefore be considered in order to speed the resolution of symptoms and infection although acute bacterial conjunctivitis is frequently self-limiting.

ATOPIC CONJUNCTIVITIS
- onset late adolescence and early adulthood with peak between 30-50 yr
- intense ocular pruritus (perennially), tearing, burning, clear mucus discharge, redness, blurry vision, photophobia, and foreign body sensation
- thickened and intermittent swelling of the eyelids, conjunctival chemosis, conjunctival hyperemia, and tarsal papillary hypertrophy
- severe cases lead to sub-epithelial fibrosis, fornix foreshortening, and corneal neovascularization, ectatic corneal disease

Treatment
- calcineurin inhibitor ointment (e.g. tacrolimus and pimecrolimus), topical cyclosporine drops, and topical corticosteroid drops

GIANT PAPILLARY CONJUNCTIVITIS (GPC)
- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva

Treatment
- clean, change, or discontinue use of contact lens, and topical corticosteroids

VERNAL CONJUNCTIVITIS
- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal shield ulcers (not infectious), limbal follicles, and keratitis
- seasonal (warm weather)
- occurs in children (often male), lasts for 5-10 yr then resolves

Treatment
- non-preserved artificial tears, consider topical steroids, topical cyclosporine (by ophthalmologist)
- shield ulcers may require debridement if topical therapy fails

VIRAL CONJUNCTIVITIS (PINK EYE)
- presents with pain and swelling
- serous discharge, lid edema, follicles, and pseudomembranes
- subepithelial corneal infiltrates
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye within a few days
- mainly due to adenovirus – highly contagious for up to 12 d

Treatment
- usually self-limiting (7-12 d)
- cool compresses, topical lubrication
- proper hygiene is important to prevent transmission

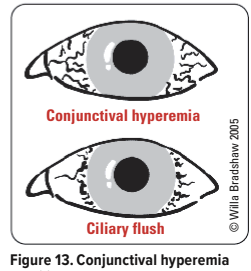


Figure 13. Conjunctival hyperemia vs. ciliary flush

BACTERIAL CONJUNCTIVITIS
- purulent discharge, lid swelling, papillae, conjunctival injection, and chemosis
- common agents include *S. aureus, S. pneumoniae, H. influenzae*, and *M. catarrhalis*
- in neonates or if sexually active must consider *N. gonorrhoeae* (can cause hyperpurulent conjunctivitis, a serious infection that may rapidly perforate cornea)
- *C. trachomatis* is the most common cause in neonates

Treatment
- topical broad-spectrum antibiotic, systemic antibiotics if indicated (especially in neonates and children)
- usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment

Enlarged lymph nodes suggest infectious etiology, especially viral or chlamydial conjunctivitis

Temporal conjunctival lymphatics drain to preauricular nodes and nasal to submandibular nodes

GONOCOCCAL AND CHLAMYDIAL CONJUNCTIVITIS
- caused by *N. gonorrhoeae* and *C. trachomatis*, respectively
- affects sexually active individuals, neonates (*Ophthalmia neonatorum*) in first 5 d of life when caused by gonorrhea (shorter incubation period) and 3-14 d of life when caused by chlamydia (longer incubation period)
- newborn prophylaxis with erythromycin 0.5% ointment
- documented or suspected cases of gonococcal conjunctivitis should be evaluated by an ophthalmologist for intensive IV and topical treatment
- chlamydia causes trachoma and inclusion conjunctivitis (different serotypes)

TRACHOMA
- leading infectious cause of blindness in the world
- associated with poor hygiene
- acute: conjunctival follicular reaction (especially in superior tarsal conjunctiva), corneal SPKs
- severe keratoconjunctivitis leads to corneal abrasion, ulceration
- chronic: scarring of tarsal conjunctiva superiorly (Arlt's line), scarring of limbal follicles (Herbert's pits), fibrovascular pannus in superior cornea, symblepharon formation, entropion of upper lid, trichiasis

Treatment
- prevention: facial cleanliness, environmental improvement
- oral antibiotics: azithromycin, doxycycline, tetracycline (contraindicated in children <8 years and pregnant or nursing mothers), or erythromycin
- topical tetracycline 1%, erythromycin
- IV ceftriaxone often given in the emergency department

INCLUSION CONJUNCTIVITIS
- chronic conjunctivitis with follicles and subepithelial infiltrates

Treatment
- oral azithromycin, tetracycline, doxycycline

Sclera
- white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

Episcleritis

Definition
- immunologically mediated inflammation of episclera
- 1/3 bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

Etiology
- mostly idiopathic
- associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, and syphilis), inflammatory bowel disease, reactive arthritis, rosacea, and atopy

To differentiate between episcleritis and scleritis, place a drop of phenylephrine 2.5% (Mydfrin®; AK-Dilate®) in the affected eye. Re-examine the vascular pattern 10-15 min later; in episcleritis the episcleral vessels should blanch with phenylephrine

Clinical Features
- may have discomfort and pain associated with red eye (often interpalpebral)
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial vessels)

Treatment
- generally self-limited, recurrent in 2/3 of cases (may need systemic work-up)
- topical steroid
- oral NSAIDs

Scleritis

- usually unilateral
- can be classified as anterior or posterior
  - anterior scleritis can be further classified as diffuse, nodular, necrotizing with inflammation, or necrotizing without inflammation (scleromalacia perforans)
  - posterior scleritis can be further classified as diffuse or nodular
- anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing
- posterior scleritis: rapidly progressive blindness, may cause exudative RD
- more common in women and elderly

Etiology
- collagen vascular disease, e.g. SLE, RA, GPA, ankylosing spondylitis
- granulomatous, e.g. tuberculosis, sarcoidosis, syphilis
- metabolic, e.g. gout, thyrotoxicosis
- infectious, e.g. *S. aureus, S. pneumoniae, P. aeruginosa*, herpes zoster
- chemical or physical agents, e.g. thermal, alkali, or acid burns
- idiopathic

Clinical Features
- severe "deep" or "boring" pain and may awaken patient at night, photophobia, red eye, decreased vision
- pain is the best indicator of disease progression
- inflammation of scleral, episcleral, and conjunctival vessels
- may have anterior chamber cells and flare, corneal infiltrate, scleral thinning, scleral edema
- posterior segment findings include subretinal fluid, optic nerve edema, macular edema
- sclera may have a purple or "violaceous" hue (best seen in natural light), due to thinning of scleral fibres exposing the bluish-coloured uvea
- failure to blanch with topical phenylephrine

Scleromalacia Perforans

Asymptomatic anterior necrotizing scleritis without inflammation

Strongly associated with RA

May result in scleral thinning

Traumatic perforation can easily occur – examine eye very gently

Treatment
- vision threatening – urgent referral to ophthalmology
- life threatening – indicator of poor systemic disease control with an increased 5 yr mortality rate (not from scleritis) without treatment of underlying untreated or unrecognized autoimmune condition
  - systemic NSAIDs, systemic steroids, subconjunctival steroids if systemic steroids are contraindicated or poorly tolerated, and systemic immunomodulation; topical difluprednate can be trialed in milder cases
- treat underlying etiology

Cornea

- function
  - transmission of light
  - refraction of light (2/3 of total refractive power of eye)
  - barrier against infection, foreign bodies
- transparency due to avascularity, uniform collagen structure, and deturgescence (relative dehydration)
- 5 layers (anterior to posterior): epithelium, Bowman's layer, stroma, Descemet's membrane, and the endothelium (dehydrates the cornea; dysfunction leads to corneal edema). Some have argued the existence of a 6th layer, "Dua's layer", although it is debated if this is a truly unique and additional layer
- extensive sensory fibre network (V1 distribution); therefore, abrasions are very painful

Learn the Layers of the Cornea
ABCDE
Anterior epithelium
Bowman's membrane
Corneal stroma
Descemet's membrane
Endothelium

Foreign Body

Definition
- foreign material in or on surface of cornea

Clinical Features
- patients may note pain, tearing, photophobia, foreign body sensation, and red eye
- signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, and anterior chamber cells/flare
- may have associated rust ring if metallic

Foreign body behind lid may cause multiple vertical corneal epithelial abrasions due to blinking

Complications
- abrasion, infection, ulcer, scarring, rust ring, secondary iritis

Treatment
- remove under magnification using local anesthetic and sterile needle or refer to ophthalmology for removal under magnification (depending on depth and location)
- treat as per corneal abrasion

Topical analgesics should only be used to facilitate examination. They should NEVER be used as treatment for any ocular problem

Corneal Abrasion

Definition
- epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (*Figure 14*)

Clinical Features (Table 7, OP19)
- pain, redness, tearing, photophobia, foreign body sensation
- de-epithelialized area stains with fluorescein dye
- pain relieved with topical anesthetic (DO NOT use for treatment – risk of corneal melt or infection)

Complications
- infection, ulceration, recurrent erosion, secondary iritis

Treatment
- topical antibiotics (drops or ointment, e.g. ciprofloxacin), abrasion in contact-lens wearing patients or from organic material should be covered against Pseudomonas (4th generation fluoroquinolones e.g. moxifloxacin)
- consider topical NSAIDs (caution due to risk of corneal melt with prolonged use), cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch (do not patch contact lens wearer or abrasions secondary to organic materials as it can precipitate infection), bandage contact lens (with proper antibiotic coverage)
- most abrasions clear spontaneously within 24-48 h

Corneal abrasions from organic matter (e.g. twig, fingernail, etc.) have higher recurrence, even years later

Patching for Corneal Abrasion
Cochrane DB Syst Rev 2016;7:CD004764
Purpose: To assess the effects of patching for corneal abrasion on healing and pain relief.
Methods: Systematic review and meta-analysis of RCTs/Quasi-RCTs that compared patching the eye with no patching to treat simple corneal abrasions.
Results: 12 RCTs/Quasi-RCTs identified, n=1080. At 24 h: people receiving patch were less likely to have a healed abrasion (RR 0.89, 95% CI 0.79-1.00). At 48 h: similar effect for both groups (RR 0.97, 95% CI 0.91-1.02). At 72 h: similar effect for both groups (RR 1.01, 95% CI 0.97-1.05).
Conclusions: Certainty of evidence is moderate to low; more research is needed with better quality trials to examine effectiveness of patching for large abrasions. Participants with patch were more likely to receive additional adjuvant treatment and took slightly longer to heal, but the difference was small and possibly clinically insignificant.

Recurrent Erosions

Definition
- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

Etiology
- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

Treatment
- same as corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment at bedtime for 6-12 mo, topical lubrication
- bandage contact lens, anterior stromal puncture, superficial keratectomy with diamond burr polishing, or phototherapeutic keratectomy for chronic recurrences

Corneal Ulcer

Etiology
- local necrosis of corneal tissue due to infection
  - infection is usually bacterial; rarely viral, fungal, or protozoan (*Acanthamoeba*)
- secondary to corneal exposure, abrasion, foreign body, or contact lens use (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

Clinical Features
- pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with an infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- conjunctival injections common; may develop corneal edema, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

Complications
- decreased vision, corneal perforation, iritis, endophthalmitis

Investigations
- Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect aqueous leaking from focal perforation; any aqueous leakage will dilute the green stain at site of wound

Treatment
- urgent referral to ophthalmology
- culture prior to treatment
- intense fortified topical antibiotics (typically vancomycin and then tobramycin) q1h
- must treat vigorously to avoid complications

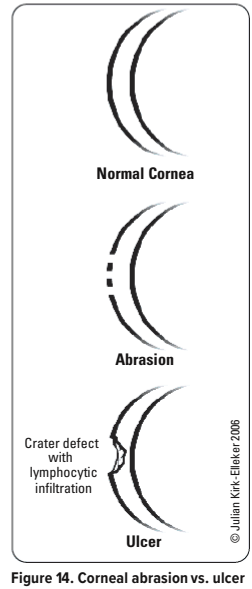


Figure 14. Corneal abrasion vs. ulcer

Table 7. Corneal Abrasion vs. Corneal Ulcer

	Abrasion	Ulcer
Time Course	Acute (instantaneous)	Subacute (days)
History of Trauma	Commonly	Rare
Cornea	Clear	White, necrotic area
Iris Detail	Clear	Obscured
Corneal Thickness	Normal	May have crater defect/thinning
Depth of Lesion	Limited to epithelium	Extension into stroma

Abrasion vs. Ulcer on Slit-Lamp
An abrasion appears clear while an ulcer is more opaque

Herpes Simplex Keratitis

- usually HSV type 1 (90% of population are carriers) but also can be type 2
- risk factor: immunosuppression

Clinical Features

- pain, tearing, foreign body sensation, red eye, decreased vision, and/or eyelid edema
- corneal hypoesthesia
- classic form of HSV infectious epithelial keratitis is a dendritic (thin and branching) lesion with terminal end bulbs in epithelium that stains with fluorescein
- other types of epithelial keratitis include geographic, margin, and neurotropic
- HSV may cause other forms of infectious epithelial keratitis, as well as stromal keratitis (which may be infectious or immune-mediated) and endotheliitis (presumably immune-mediated but possible role of live virus)

Complications

- corneal scarring (can lead to loss of vision) and hypoesthesia
- chronic interstitial keratitis due to penetration of virus into stroma
- secondary iritis, secondary glaucoma

Treatment

- systemic antiviral such as acyclovir, valacyclovir, famciclovir
- topical antiviral such as ganciclovir ophthalmic gel 0.15%
- trifluridine ophthalmic solutions 1% are generally not first line due to corneal toxicity
- debridement of dendrite
- no steroids initially for epithelial disease – may exacerbate condition
- ophthalmologist must exercise caution if adding topical steroids for stromal keratitis, endotheliitis or iritis
- patients may require antiviral prophylaxis (duration for at least 1 year) if there are multiple recurrences of HSV keratitis, especially HSV stromal keratitis, recurrent inflammation with scarring or vascularization approaching visual axis, >1 episode of HSV keratitis with ulceration

Steroid treatment for ocular disorders should only be prescribed and supervised by an ophthalmologist, as they can impair corneal healing, exacerbate herpetic keratitis, and elevate IOP

Herpes Zoster Ophthalmicus

Definition

- dermatitis in the dermatomal distribution of CN V1 that is typically unilateral and respects the midline
- Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then globe will be involved in ~75% of cases
- if no nasal involvement, eye is involved in 1/3 of patients

Clinical Features

- pain, tearing, photophobia, and red eye
- corneal edema, pseudodendrite, and SPK
- corneal hypoesthesia

Complications

- sclerokeratitis, corneal ulceration, perforation, and scarring
- secondary iritis, secondary glaucoma, cataract
- posterior segment: acute retinal necrosis, papillitis, retrobulbar optic neuritis
- muscle palsies (rare) due to cavernous sinus involvement
- occasionally severe post-herpetic neuralgia

Treatment

- oral antiviral (acyclovir, valacyclovir, or famciclovir) immediately
- topical steroids, cycloplegia as indicated for immune-mediated keratitis, iritis
- prevention: vaccination in immunocompetent patients

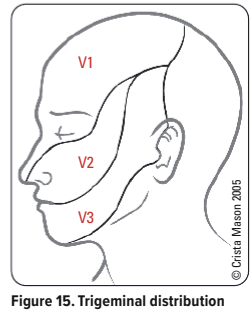


Figure 15. Trigeminal distribution

Keratoconus

Definition
- bilateral (usually asymmetric) thinning and bulging (ectasia) of the cornea resulting in a conical shape
- usually sporadic but can be associated with Down syndrome, atopy, contact lens use, and chronic eye rubbing
- associated with breaks in Descemet's membrane and Bowman's layer
- results in decreased vision from irregular astigmatism, scarring, and stromal edema

To detect keratoconus, look for bulging of the lower eyelid when the patient looks downward (Munson's sign)

Treatment
- attempt correction with spectacles and/or rigid gas permeable or scleral contact lens
- corneal collagen cross-linking treatment to halt disease progression
- intrastromal corneal ring segments can help flatten the corneal cone
- penetrating keratoplasty or deep anterior lamellar keratoplasty (partial-thickness corneal transplant) as last resort

Arcus Senilis

- hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
- common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
- may be associated with hypercholesterolemia if age <40 yr, check lipid profile
- no associated visual symptoms, complications, or treatment necessary

Kayser-Fleischer Ring

- brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
- due to deposition of copper pigment in Descemet's membrane
- associated with Wilson's disease
- no associated symptoms or complications of ring
- treat underlying disease

The Uveal Tract

- uveal tract (from anterior to posterior) = iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina

Uveitis

- uveal inflammation which may involve one, two, or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, and malignant causes
- should be managed by an optometrist or ophthalmologist
- anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis based on primary site of inflammation

Table 8. Anatomic Classification of Uveitis

	Anterior Uveitis (Iritis)	Intermediate Uveitis	Posterior Uveitis
Location	Inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), both = iridocyclitis Usually unilateral	The vitreous is the major site of the inflammation	Inflammation of the choroid (choroiditis), retina (retinitis), or both (chorioretinitis)
Etiology	Usually Usually idiopathic Connective tissue diseases: HLA-B27: reactive arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease Non-HLA-B27: juvenile idiopathic arthritis Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster Other: sarcoidosis, tubulointerstitial nephritis, and uveitis syndrome (TINU), trauma, large corneal abrasion, and postocular surgery	Mostly idiopathic, secondary causes include sarcoidosis, multiple sclerosis, tubulointerstitial nephritis and uveitis syndrome (TINU) Infectious: Lyme, syphilis, TB	Bacterial: syphilis, tuberculosis Viral: herpes simplex/zoster virus, CMV in AIDS Fungal: histoplasmosis, candidiasis Parasitic: toxoplasmosis (most common cause), toxocara Immunosuppression may predispose to any of the above infections Autoimmune: Behçet's disease (triad of oral ulcers, genital ulcers, and posterior uveitis) Malignancies (masquerade syndrome): metastatic lesions, malignant melanoma, lymphoma
Clinical Features	Photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased VA, lacrimation Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle) Anterior chamber "cells" (WBC in anterior chamber due to anterior segment inflammation) and "flare" (light reflection from the protein in anterior chamber secondary to breakdown of blood-aqueous barrier), hypopyon (collection of neutrophilic cells/exudate inferiorly in the anterior chamber) Occasionally keratic precipitates (clumps of cells on corneal endothelium) Iritis typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis or iritis from herpes simplex and zoster may cause inflammatory glaucoma (trabeculitis)	Insidious onset of blurred vision, accompanied by vitreous floaters Initial symptoms are usually unilateral but inflammation is usually bilateral and asymmetric Associated with anterior uveitis, most severe cases of secondary intermediate uveitis Vitreous cells, snowballs (vitreous aggregates of inflammatory cells at pars plana) 'snowbank' = gliosis of the pars plana	Painless Often no conjunctival or scleral injection present Decreased VA Floaters (debris and inflammatory cells) Vitreous cells and opacities Hypopyon formation

Table 8. Anatomic Classification of Uveitis

	Anterior Uveitis (Iritis)	Intermediate Uveitis	Posterior Uveitis
Complications	Inflammatory glaucoma Posterior synechiae Adhesions of posterior iris to anterior lens capsule Indicated by an irregularly shaped pupil If occurs 360°, can lead to angle closure glaucoma Peripheral anterior synechiae (rare) Adhesions of iris to cornea Can lead to secondary angle closure glaucoma Cataracts (usually posterior subcapsular) Band keratopathy - superficial corneal calcification (seen in chronic iritis) Macular edema with chronic iritis Papillitis	Cystoid macular edema (30% of cases), cataract, and glaucoma Papillitis Neovascularization Vitreous hemorrhage (uncommon)	Macular edema Neovascularization if there is significant occlusive vasculitis and retinal ischemia Retinal detachment Visual field loss/scotoma
Treatment	Mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm Steroids: topical, sub-tenon, or systemic Systemic immunosuppressants in refractory cases If recurrent episodes, medical workup may be indicated to rule out secondary causes	After ruling out infectious etiologies: sub-tenon/intravitreal steroid for asymmetric or unilateral cases, systemic steroids for bilateral cases, and immunosuppressive agents Vitrectomy, cryotherapy, or laser photocoagulation to the "snowbank"	After ruling out infectious etiologies: Steroids: sub-tenon, intravitreal, or systemic if indicated (e.g. threat of vision loss) Vitreous biopsy if suspected masquerade/malignancy

Lens

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

Cataracts

Definition
- any opacity of the lens, regardless of etiology
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, and posterior subcapsular

Etiology
- acquired
  - age-related (over 90% of all cataracts)
  - cataract associated with systemic disease (may have juvenile onset)
    - DM
    - metabolic disorders (e.g. Wilson's disease, galactosemia, or homocystinuria)
    - hypocalcemia
  - traumatic (may be rosette-shaped)
  - intraocular inflammation (e.g. uveitis)
  - toxic (steroids, phenothiazines)
  - radiation
- congenital
  - high myopia
  - present with altered red reflex or leukocoria
  - treat promptly to prevent amblyopia

Clinical Features
- gradual, painless, progressive decrease in VA
- glare, dimness, halos around lights at night, monocular diplopia
- "second sight" phenomenon (myopic shift): patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
  - patient may present with new/increased near-sightedness
- diagnosis by slit-lamp exam
- may impair view of retina during fundoscopy

Treatment
- posterior capsular opacification may occur in 20-50% of patients post-cataract surgery
- may be treated with YAG laser capsulotomy
- surgical: definitive treatment
  - indications for surgery
    - to improve visual function in patients whose vision loss leads to functional impairment
    - to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
    - congenital or traumatic cataracts
  - phacoemulsification (phaco = lens)
    - most commonly used surgical technique
    - postoperative complications: RD, endophthalmitis, dislocated IOL, macular edema, glaucoma, posterior capsular opacification

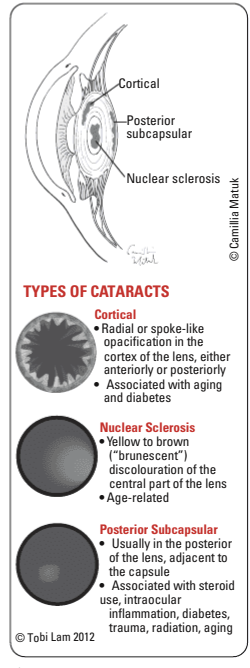

Cortical
Posterior subcapsular
Nuclear sclerosis
© Camillia Matuk
TYPES OF CATARACTS
Cortical
• Radial or spoke-like opacification in the cortex of the lens, either anteriorly or posteriorly
• Associated with aging and diabetes
Nuclear Sclerosis
• Yellow to brown ("brunescent") discolouration of the central part of the lens
• Age-related
Posterior Subcapsular
• Usually in the posterior of the lens, adjacent to the capsule
• Associated with steroid use, intraocular inflammation, diabetes, trauma, radiation, aging
© Tobi Lam 2012

Figure 16. Types of cataracts

Dislocated Lens (Ectopia Lentis)

Etiology
- associated with Marfan Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic

Clinical Features
- decreased VA
- may get monocular diplopia
- iridodonesis (quivering of iris with movement)
- phacodonesis (observed movement of the lens)
- direct fundoscopy may elicit abnormal red reflex

Complications
- cataract, glaucoma, and uveitis

Treatment
- surgical lens replacement if affecting vision

Vitreous

- clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, vitreous base (pars plana/ora serrata), and along major retinal blood vessels

Posterior Vitreous Detachment

Etiology
- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, vitreous fibrils condense causing vitreous floaters
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

Clinical Features
- floaters, flashes of light

Complications
- traction at sites of firm adhesion may result in retinal tear with or without subsequent rhegmatogenous retinal detachment
- retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
- complications more common in high myopes and following ocular trauma (blunt or perforating)

Treatment
- acute onset of PVD requires a dilated fundus exam to rule out retinal tears/detachment
- floaters may be treated with vitrectomy or YAG laser vitreolysis, although treatment is not recommended in most cases

Weiss Ring: formed by glial tissue around the optic disc that remains attached to the detached posterior vitreous

Floaters: "bugs", "cobwebs", or "spots" of vitreous condensation that move with eye position

Although most floaters are benign, new or markedly increased floaters or flashes of light require a dilated fundus exam to rule out retinal tears/detachment

Vitreous Hemorrhage

Definition
- bleeding into the vitreous cavity

Etiology
- PDR
- retinal tear/detachment
- PVD
- retinal vein occlusion
- trauma

Any time a vitreous or retinal hemorrhage is seen in a child, must consider child abuse

Clinical Features
- sudden loss of VA
- may be preceded by "shower" of many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

Treatment
- ultrasound (B-scan) to rule out RD
- expectant: in non-urgent cases (e.g. no RD), blood usually resorbs in 3-6 mo
- surgical: vitrectomy ± RD repair ± retinal endolaser for bleeding sites/retinal tears

Endophthalmitis and Vitritis

Definition
- intraocular infection: acute, subacute, or chronic

Etiology
- most commonly as postoperative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal

Clinical Features
- painful, red eye, photophobia, discharge
- severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, chemosis, hyphema, decreased IOP, etc.)

Treatment (see Ocular Trauma, OP41)
- **OCULAR EMERGENCY**: presenting vision indicates prognosis
- LP or worse: admission, immediate vitrectomy, and intravitreal antibiotics to prevent loss of vision
- HM or better: vitreous tap for culture and intravitreal antibiotics
- topical fortified antibiotics

Remember to inquire about tetanus status in post-traumatic endophthalmitis

Retina

- composed of two parts (see *Figure 2, OP2*)
  - neurosensory retina: comprises 9 of the 10 retinal layers, including photoreceptors and ganglion cell layer
  - RPE layer: external to neurosensory retina
- macula: rich in cones (for colour vision), most sensitive area of retina
- fovea: centre of macula, responsible for detail, fine vision, lacks retinal vessels
- optic disc: collection of retinal nerve fibre layers forming optic nerve (CN II)
- ora serrata: irregularly-shaped, anterior margin of the retina (cannot be visualized with direct ophthalmoscope, but possible with indirect ophthalmoscope/scleral depression)

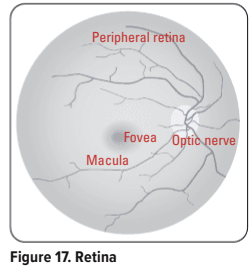


Figure 17. Retina

Central/Branch Retinal Artery Occlusion

Etiology
- occlusion of blood flow from the following causes results in loss of vision due to oxygen starvation of the retinal tissues and eventual cell death
  - emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
  - thrombus
  - GCA/temporal arteritis

Clinical Features
- sudden, painless (except in GCA), severe monocular loss of vision
- RAPD in CRAO or large BRAO
- patient may have experienced transient episodes in the past (amaurosis fugax)
- fundoscopy
  - "cherry-red spot" (see *Figure 18, OP24*)
  - retinal edema
  - cotton wool spots (retinal infarcts)
  - cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations

Treatment
- **OCULAR EMERGENCY**: attempt to restore blood flow within 2 h (irreversible retinal damage if >90 min of complete CRAO)
- massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
- decrease IOP
  - topical β-blocker
  - IV acetazolamide
  - IV mannitol (draws fluid from eye)
  - drain aqueous fluid – anterior chamber paracentesis (carries risk of infection, lens puncture)
- YAG laser embolectomy
- intra-arterial or intravenous thrombolysis
- hyperbaric oxygen therapy
- urgent neurology referral, optimize vascular risk factors (e.g. smoking cessation), anticoagulation/antiplatelet, carotid artery duplex ultrasonography, and possible vascular surgery referral

Hallmark of CRAO
"Cherry-red spot" located at centre of macula (visualization of unaffected highly vascular choroid through the thin fovea)

Treatment for a CRAO must be initiated within 2 h of symptom onset for any hope of restoring vision

The "blood and thunder" appearance on fundoscopy is very specific for CRVO

There is an 8-10% risk of developing CRVO or BRVO in the other eye

Central/Branch Retinal Vein Occlusion

Etiology
- second most frequent "vascular" retinal disorder after DR
- exact cause is not known; possible arteriosclerotic changes in the central retinal artery transform the artery into a rigid structure and impinge upon the central retinal vein as they share a common sheath
- predisposing factors: atherosclerotic vascular disease, HTN, DM, glaucoma, hyperviscosity (e.g. sickle cell disease, polycythemia rubra vera, lymphoma, leukemia), drugs (e.g. oral contraceptive pill, diuretics)

Clinical Features
- painless, monocular, gradual, or sudden vision loss
- ± RAPD
- fundoscopy
  - "blood and thunder" appearance (see *Figure 18*)
  - diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - no RAPD, VA ~20/80
    - mild hemorrhage, few cotton wool spots
    - resolves spontaneously over weeks to months
    - may regain normal vision if macula unaffected
  - hemorrhagic/ischemic retinopathy
    - usually older patient with deficient arterial supply
    - RAPD, VA ~20/200, reduced peripheral vision
    - more hemorrhages, cotton wool spots, venous congestion
    - poor visual prognosis

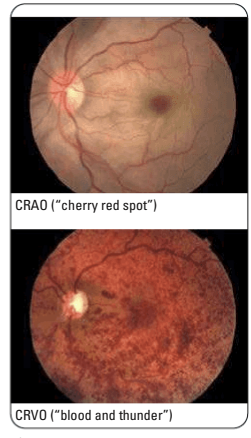
Complications
- neovascularization of retina and iris (secondary rubeosis), may lead to secondary glaucoma
- vitreous hemorrhage
- macular edema

Treatment
- retinal laser photocoagulation, anti-VEGF, and/or corticosteroid injection
- optimize systemic risk factors (BP, lipids) and consider systemic work-up for patients without risk factors

Retinal Detachment

Definition
- cleavage in the plane between the neurosensory retina and the RPE
- three types
  - rhegmatogenous (most common)
    - caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - tears may be caused by PVD, degenerative retinal changes, trauma, or iatrogenic complications
    - incidence increases with advancing age, in high myopes, and after ocular surgery/trauma
  - tractional
    - caused by vitreal, epiretinal, or subretinal membrane pulling the neurosensory retina away from the underlying RPE
    - found in conditions such as DR, RVO, sickle cell disease, ROP, and ocular trauma
  - exudative
    - caused by vascular transudation of fluid or damage to the RPE resulting in fluid accumulation in the subretinal space
    - main causes are intraocular tumour, posterior uveitis, central serous retinopathy

Clinical Features
- sudden onset
- flashes of light
  - due to mechanical stimulation of the retinal photoreceptors
- floaters
- hazy spots in the line of vision which move with eye position
  - due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/peripheral field loss
  - darkness in the field of vision where the retina has detached
- loss of central vision (if macula "off")
- decreased IOP (usually 4-5 mmHg lower than the other, unaffected eye)
- fundoscopy: detached retina is grey-white from retinal edema, and loss of red reflex
- ± RAPD


CRAO ("cherry red spot")

CRVO ("blood and thunder")

Figure 18. Fundus photographs of CRAO ("cherry red spot") and CRVO ("blood and thunder")

Effect of Bevacizumab vs. Aflibercept on Visual Acuity among Patients with Macular Edema due to Central Retinal Vein Occlusion – The SCORE2 Randomized Clinical Trial
JAMA 2017;317(20):2072-2087
Purpose: To investigate whether bevacizumab (used off-label) is non-inferior to aflibercept for the treatment of macular edema secondary to central retinal or hemiretinal vein occlusion.
Methods: 362 patients with macular edema due to central retinal or hemiretinal vein occlusion were randomized to either the bevacizumab-treatment group or the aflibercept-treatment group.
Results: At 6 mo, the mean VA letter score (VALS) was 69.3 (a mean increase from baseline of 18.6) in the bevacizumab group and 69.3 (a mean increase from baseline of 18.9) in the aflibercept group ($P = 0.001$ for noninferiority). Adverse events were rare but were similar between the two groups.
Conclusion: After 6 mo of treatment, bevacizumab was non-inferior to aflibercept with respect to VA. Cost differences between the drugs have important economic implications.

Integrated Results from the COPERNICUS and GALILEO Studies
Clin Ophthalmol 2017;11:1533-1540
Purpose: Comparing the effects of intravitreal aflibercept to sham injection for macular edema caused by CRVO.
Methods: COPERNICUS (n=187) and GALILEO (n=171) were parallel, double-blind, Phase III RCTs. In the COPERNICUS trial, patients in the sham group crossed over to the treatment group at 24-52 wk of the trial. Patients in the GALILEO trial receiving the sham treatment continued to receive sham injections every 4 wk between 24 wk and 52 wk.
Conclusion: Prompt treatment with intravitreal aflibercept is an effective treatment for macular edema following CRVO.

Treatment
- prophylactic: symptomatic tear (flashes or floaters) can be sealed off with laser/cryotherapy
- therapeutic:
  - rhegmatogenous
    - scleral buckle procedure
    - pneumatic retinopexy
    - pars plana vitrectomy plus injection of gas (injection of silicone oil in cases of recurrent detachment, air travel, or inability to posture postoperative)
  - tractional
    - vitrectomy ± membrane removal/scleral buckling/injection of intraocular gas or silicone oil as necessary
  - exudative
    - management is nonsurgical; any underlying disease should be treated if possible

Complications
- loss of vision, vitreous hemorrhage, recurrent RD
- RD is an emergency, especially if the macula is still attached ("macula on")
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

Retinitis Pigmentosa

Definition
- hereditary degenerative disease of the retina manifested by photoreceptor degeneration (rods affected to a greater extent than cones) and atrophy
- many forms of inheritance, most commonly autosomal recessive (60%)

Clinical Features
- night blindness, decreased peripheral vision ("tunnel vision"), decreased central vision (macular changes), glare (from posterior subcapsular cataracts, common)

Investigations
- fundoscopy: areas of "bone-spicule" pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
- electrophysiological tests: electroretinography (ERG) and electrooculography (EOG)

Treatment
- gene treatments have the potential to reverse the condition; cataract extraction improves visual function
- vitamin A supplementation can reduce progression of disease in some patients; avoid vitamin E supplementation
- Voretigene neparvovec-rzyl (Luxturna®) is an FDA-approved novel gene therapy for pediatric and adult patients with biallelic RPE65 mutation-associated retinal dystrophy

Age-Related Macular Degeneration

Definition
- leading cause of irreversible blindness in industrialized countries, associated with increasing age, usually bilateral but asymmetric

Classification
- **Non-Exudative/"Dry" (Non-Neovascular) AMD**
  - most common type of AMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow deposits between the RPE and Bruch's membrane
  - geographic atrophy: coalescence of RPE atrophy, clumps of focal hyperpigmentation or hypopigmentation
  - may progress to neovascular AMD
- **Exudative/"Wet" (Neovascular) AMD**
  - 10% of AMD cases; however, responsible for 80% of AMD-related vision loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch's membrane causing subsequent growth and proliferation of new, fine choroidal vessels
  - may lead to exudative detachment of overlying RPE and retina, hemorrhage, and lipid precipitates into the subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of subretinal fibrovascular proliferation that progresses to disciform scarring and severe central vision loss

Efficacy and Safety of Widely Used Treatments for Macular Edema Secondary to Retinal Vein Occlusion: A Systematic Review
BMC Ophthalmol 2014;14:17
Purpose: To assess the efficacy of widely used treatments for macular edema (ME) secondary to retinal vein occlusion (RVO). ME secondary to RVO can cause vision loss due to CRVO or a BRVO.
Outcomes: Mean change in BCVA from baseline and/or number of patients gaining at least 10 letters from baseline to 6 mo or equivalent time point.
Results: 14 unique RCTs identified. Ranibizumab 0.5 mg produced greater improvements in BCVA at 6 mo compared to sham in BRVO (mean difference 11 letters; 95% CI 7.83-14.17) and CRVO (mean difference 14 letters; 95% CI 10.51-17.69). Improvements in BCVA were also observed with dexamethasone 0.7 mg intravitreal implant (IVT) compared with sham in patients with BRVO or CRVO (mean difference 2.5 letters; 95% CI 0.7-4.3). The difference was significant with BRVO alone, but not CRVO alone. At 36 mo in a large prospective RCT, a greater proportion of patients with BRVO gained >15 letters with laser therapy vs. no treatment (OR 3.16; 95% CI 1.25-8.00), whereas no difference was observed in a 9 mo endpoint in a smaller study. Three studies showed no benefit for laser therapy in CRVO.
Conclusion: Both IVT ranibizumab and dexamethasone show significant improvements over previously accepted standard of care (laser therapy) for the treatment of BRVO and CRVO.

Superotemporal retina is the most common site for horseshoe tears

Retinitis Pigmentosa Inherited Forms
- Autosomal recessive: most common
- Autosomal dominant: best prognosis
- X-linked: worst prognosis

Triad of Retinitis Pigmentosa
APO
Arteriolar narrowing
Perivascular bone spicule pigmentation
Optic disc pallor

Risk Factors
- female
- increasing age
- family history
- smoking
- White individuals
- blue irides

Clinical Features
- variable degree of progressive central vision loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

Investigations
- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography: assesses type and location of choroidal neovascularization – pathologic new vessels leak dye
- OCT retinal imaging: assesses the amount of intraretinal and subretinal exudation

Treatment
- **non-neovascular "dry" AMD**
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed-circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visors
  - see Age-related Eye Disease Study 2 (AREDS2) in sidebar
- **neovascular "wet" AMD**
  - see *Common Medications, OP44*
  - intravitreal injection of anti-VEGF
    - ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea®), pegaptanib (Macugen®), brolucizumab (Beovu®), faricimab (Vabysmo®) (see *VEGF Inhibitors, OP45*)
  - no definitive treatment for disciform scarring
  - photodynamic therapy with verteporfin (Visudyne®)
    - IV injection of verteporfin, followed by low-intensity laser to area of choroidal neovascularization

Age-Related Eye Disease Study 2 (AREDS2) Lutein + Zeaxanthin and Omega-3 Fatty Acids for AMD: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial
JAMA 2013;309(19):2005-2015
See Landmark Ophthalmology Trials table for more information on Age-Related Eye Disease Study 2 (AREDS2), which details whether adding lutein + zeaxanthin, docosahexanoic acid (DHA) + eicosapentanoic acid (EPA), or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating β-carotene, lowering zinc doses, or both in the AREDS formulation in patients at risk for advanced AMD.

Ten Year Follow-Up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study: AREDS Report No. 36
JAMA Ophthalmol 2014;132(3):272-277
Study: Randomized clinical trial.
Purpose: To describe 10 yr progression rates to intermediate or advanced AMD.
Patients: Age-related eye disease study (AREDS) participants were observed for an additional 5 yr after RCT completion. Participants ages 55-80 yr with no AMD or AMD of varying severity (n=4757) were followed up in the AREDS trial for a median duration of 6.5 yr. When the trial ended, 3549 of the 4203 surviving participants were followed for 5 additional yr.
Intervention: Treatment with antioxidant vitamins and minerals.
Main Outcome: Development of varying stages of AMD and changes in VA.
Results: The risk of progression to advanced AMD increased with increasing age (P=0.01) and severity of drusen. Women (P=0.005) and current smokers (P<0.001) were at increased risk of neovascular AMD. In the oldest participants with the most severe AMD status at baseline, the risks of developing neovascular AMD and central geographic atrophy by 10 yr were 48.1% and 26.0%, respectively. Similarly, rates of progression to large drusen increased with increasing severity of drusen at baseline, with 70.9% of participants with bilateral medium drusen progressing to large drusen and 13.8% to advanced AMD in 10 yr. Median VA at 10 yr in eyes that had large drusen at baseline but never developed advanced AMD was 20/25; eyes that developed advanced AMD had a median VA of 20/200.
Conclusion: The natural history of AMD demonstrates relentless loss of vision in persons who developed advanced AMD.

Glaucoma

Definition
- progressive, irreversible, pressure-sensitive optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

Background
- aqueous is produced by the ciliary body and drains into the episcleral veins via the trabecular meshwork and Canal of Schlemm
- an isolated increase in IOP is termed ocular hypertension (OHT) - should be followed for increased risk of developing glaucoma
- IOP >21 mmHg increases the risk of developing glaucoma
- central corneal thickness is important when interpreting the IOP (e.g. thicker cornea will result in overestimation of the IOP)
- loss of peripheral vision most commonly precedes central vision loss
- structural changes commonly precede functional changes

Investigations
- VA testing
- slit-lamp exam to assess anterior chamber depth; gonioscopy to assess angle (open or closed)
- fundoscopy to assess the disc features
- tonometry to measure IOP
- automated perimetry (formal visual field testing)
- pachymetry to measure corneal thickness
- OCT of the retinal nerve fibre layer (NFL) at the optic nerve to monitor for loss of NFL
- OCT of the macular ganglion cell layer-inner plexiform layer (GCIPL) to monitor for loss of GCIPL
- follow-up includes optic disc examination, IOP measurement, OCT of the retinal NFL and macular GCIPL, and visual field testing to monitor course of disease

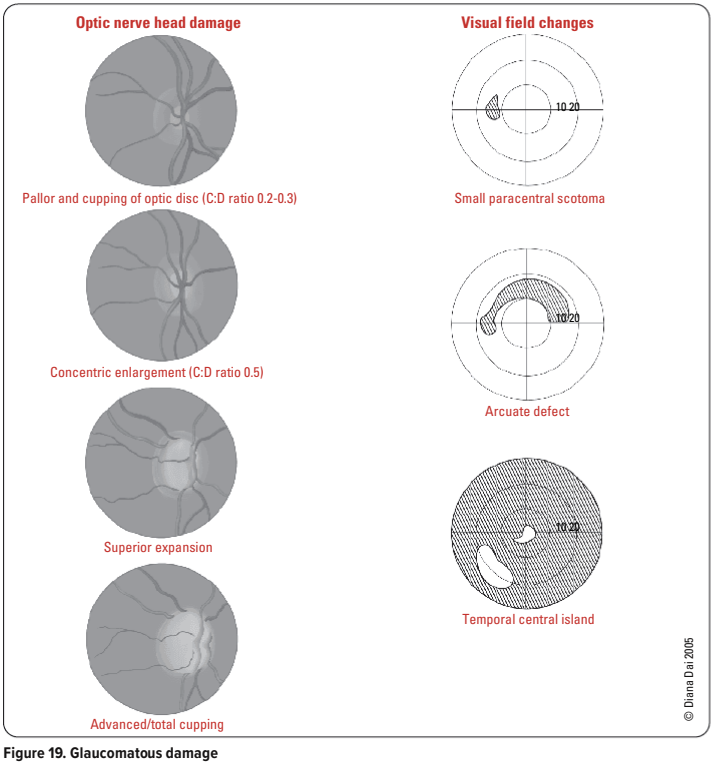


Figure 19. Glaucomatous damage

Average IOP: 15±3 mmHg
Normal CDR: ≤0.4
Suspect glaucoma if CDR >0.6, CDR differs between eyes by >0.2, or cup approaches disc margin

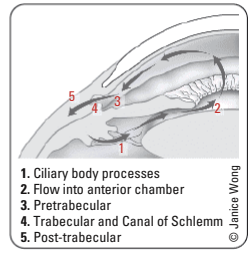


Figure 20. Aqueous flow and sites of potential resistance

Primary Open-Angle Glaucoma

Definition
- most common type, >95% of all glaucoma cases
- unobstructed open-angle, resistance is within the trabecular meshwork
- insidious and asymptomatic, screening is critical for early detection

Major Risk Factors
- ocular hypertension (IOP >21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic
- thin central cornea (OHTS trial)

Minor Risk Factors
- myopia
- HTN
- DM
- hyperthyroidism (Graves' disease)
- chronic corticosteroid use (topical significantly higher risk than oral)
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

Clinical Features
- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased CDR (vertical CDR >0.6)
  - significant CDR asymmetry between eyes (>0.2 difference)

Risk Factors for POAG
A FIAT
Age
Family history
IOP
African descent
Thin cornea

Open- and Closed-Angle Glaucoma

POAG	PACG
Common (95%)	Rare (5%)
More common in Black and Hispanic individuals	More common in Asian and Indigenous Canadians
Chronic course	Acute or chronic onset
Painless eye without redness	Painful red eye
Moderately high IOP	Extremely high IOP
Normal cornea and pupil	Hazy cornea Mid-dilated pupil unreactive to light
No N/V	±N/V, abdominal pain
No halos around light	Halos around light

- thinning, notching of the neuroretinal rim
- flame-shaped disc hemorrhage
- 360° of peripapillary atrophy
- NFL defect
- large vessels become nasally displaced
- retinal NFL vertical thinning on OCT
- GCIPL thinning on OCT

- visual field loss
- slow, progressive, irreversible loss of peripheral vision
- paracentral defects, arcuate scotoma, and nasal step are characteristics (see *Figure 19, OP27*)
- late loss of central vision if untreated

Treatment

- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see *Table 14, Glaucoma Medications, OP44*)
  - increase aqueous outflow
    - topical prostaglandin analogues
    - topical α2-adrenergics
    - topical cholinergics/parasympathomimetics
  - decrease aqueous production
    - topical β-blockers
    - topical and oral carbonic anhydrase inhibitors
    - topical α2-adrenergics
- laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
- trabeculectomy: creation of a new outflow tract from anterior chamber to under the conjunctiva forming a bleb
- minimally invasive glaucoma surgery (MIGS): implantation of IOP lowering drainage devices (e.g. iStent, Xen, Hydrus); high safety profile, primarily used for modest IOP reductions in patients with mild-to-moderate glaucoma
- tube shunt (Ahmed, Baerveldt): for advanced stages of glaucoma
- serial optic nerve head examinations, IOP measurements, OCT of retinal NFL and GCIPL, and visual field testing to monitor disease course

Elevated IOP is the only modifiable risk factor that has been proven to prevent progression of glaucoma. Treating patients with ocular hypertension but no signs of glaucoma has also been shown to reduce the risk of developing glaucoma.

The Ocular Hypertension Treatment Study
Arch Ophthalmol-Chic 2002;120:701-713
See Landmark Ophthalmology Trials table for more information on The Ocular Hypertension Treatment Study, which details the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of POAG.

Normal Tension Glaucoma

Definition

- glaucomatous optic neuropathy with IOP in normal range
- often found in women >60 yr, but may occur earlier
- associated with migraines, peripheral vasospasm, systemic nocturnal hypotension, and sleep apnea
- damage to optic nerve may be due to vascular insufficiency

Treatment

- treat reversible causes
- lower intraocular pressure

Secondary Open-Angle Glaucoma

Definition

- increased IOP secondary to ocular/systemic disorders that obstruct the trabecular meshwork including:
  - steroid-induced glaucoma: topical, periocular, and even systemic or inhalational routes can induce open angle glaucoma, primarily due to reduced facility of aqueous outflow
  - traumatic glaucoma: both blunt and penetrating injuries leave damaged tissues and scarring that may obstruct drainage channels and potentially raise IOP immediately after the injury or years later
  - pigmentary glaucoma: a result of pigment dispersion syndrome, which is characterized by aberrant iridozonular contact leading to iris pigment dispersion throughout the anterior segment and deposition into the trabecular meshwork
  - pseudoexfoliation glaucoma: a result of pseudoexfoliation syndrome, an age-related systemic disorder where extracellular fibrillar deposits progressively accumulate over various tissues, including the anterior segment of the eye

Rule of Fours
1/4 of general population using topical steroid for 4 wk, 4x/d will develop an increase in IOP

Primary Angle-Closure Glaucoma

Definition

- 5% of all glaucoma cases
- peripheral iris bows forward obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block and results in impaired drainage, leading to a sudden rise in IOP

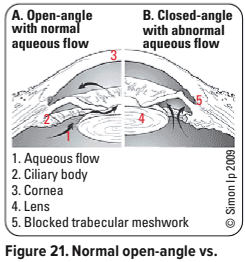


Figure 21. Normal open-angle vs. angle-closure glaucoma

Risk Factors
- hyperopia: small eye, big lens – large lens crowds the angle
- age >70 yr
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

Clinical Features
- red, painful eye with acute presentation = **RED FLAG**
- unilateral, but other eye at increased risk
- decreased VA, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

Complications
- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae, resulting in permanent angle closure

Treatment
- **OCULAR EMERGENCY**: refer to ophthalmologist for acute angle-closure glaucoma
- medical treatment (see *Table 14, Glaucoma Medications, OP44*)
  - aqueous suppressants and hyperosmotic agents such as oral glycerine or IV mannitol
  - miotic drops (pilocarpine) to reverse pupillary block
  - multiple topical IOP-lowering agents
- laser iridotomy is definitive

Angle-Closure Glaucoma

BACH
Tx with miotics and **β-b**lockers
Adrenergics
Cholinergics
Hyperosmotic agents

Collaborative Normal Tension Glaucoma Study
Curr Opin Ophthalmol 2003;14:86-90
Treatment aimed at lowering IOP by 30% in patients with normal tension glaucoma tends to reduce the rate of visual field loss. Due to variability in disease progression and a significant group that shows no visual field loss at 5 yr despite no treatment, further studies are needed to delineate which subgroups may benefit most from treatment.

Secondary Angle-Closure Glaucoma

Uveitis
- inflamed iris adheres to lens (posterior synechiae)

Neovascular Glaucoma
- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with PDR or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris and angle vessels

Pupils

- pupil size is determined by a delicate balance between the sphincter and dilator muscle tone
- sphincter muscles are innervated by the parasympathetic nervous system carried by CN III
- dilator muscles are innervated by the sympathetic nervous system (SNS)
  - first-order neuron = hypothalamus → brainstem → spinal cord
  - second-order/preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
  - third-order/postganglionic fibres originate in the superior cervical ganglion, neurotransmitter is norepinephrine
- see Neurology, Figure 8, N8

5 Targets of Retinal Signals
Pretectal nucleus (pupillary reflex/eye movements)
Lateral geniculate body of thalamus
Superior colliculus (eye movements)
Suprachiasmatic nucleus (optokinetic)
Accessory optic system (circadian rhythm)

Pupillary Light Reflex

- light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → midbrain
- impulses enter bilaterally in midbrain via pretectal area and Edinger-Westphal nuclei
- nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes
- receptors involved:
  - α1 – pupillary dilator muscle contraction (mydriasis)
  - β2 – ciliary muscle relaxation (non-accommodation); increased aqueous humour production
  - M3 – pupillary sphincter contraction (miosis); increased ciliary muscle contraction (accommodation)

Pupil Abnormalities

Denervation Hypersensitivity

- when postganglionic fibres are damaged, the under-stimulated end-organ attempts to compensate by developing an increase of neuroreceptors and becomes hypersensitive
- postganglionic parasympathetic lesions (i.e. Adie's pupil)
  - pupil will constrict with pilocarpine 0.125% (cholinergic agonist), normal pupil will not
  - pupil constricts to a near target (light-near dissociation)
- postganglionic sympathetic lesions (i.e. Horner's syndrome)
  - Horner's pupil will dilate with apraclonidine 0.5-1%, normal pupil will not (reversal of anisocoria)

Local Disorders of Iris

- posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
- ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o'clock positions resulting in a vertically oval pupil that reacts poorly to light
- trauma (e.g. blunt trauma or post-intraocular surgery)

Anisocoria

- unequal pupil size
- idiopathic/physiologic anisocoria
  - 20% of population
  - round, regular, <1 mm difference
  - pupils reactive to light and a near target
  - responds normally to mydriatics/miotics
  - post eye surgery or extensive retinal laser treatment

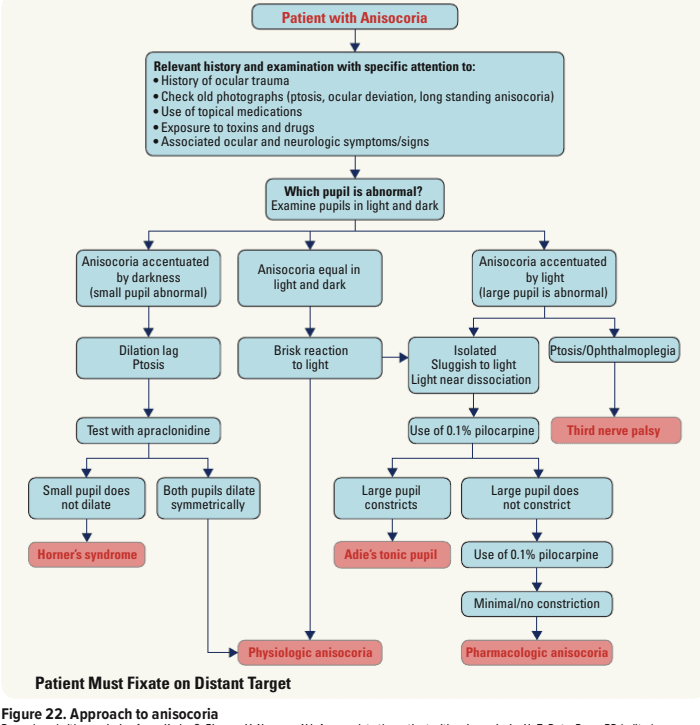

Patient with Anisocoria
Relevant history and examination with specific attention to:
• History of ocular trauma
• Check old photographs (ptosis, ocular deviation, long standing anisocoria)
• Use of topical medications
• Exposure to toxins and drugs
• Associated ocular and neurologic symptoms/signs
Which pupil is abnormal?
Examine pupils in light and dark
Anisocoria accentuated by darkness (small pupil abnormal)
Anisocoria equal in light and dark
Anisocoria accentuated by light (large pupil is abnormal)
Dilation lag
Ptosis
Brisk reaction to light
Isolated
Sluggish to light
Light near dissociation
Ptosis/Ophthalmoplegia
Test with apraclonidine
Use of 0.1% pilocarpine
Third nerve palsy
Small pupil does not dilate
Both pupils dilate symmetrically
Large pupil constricts
Large pupil does not constrict
Horner's syndrome
Adie's tonic pupil
Use of 0.1% pilocarpine
Minimal/no constriction
Physiologic anisocoria
Pharmacologic anisocoria
Patient Must Fixate on Distant Target

Figure 22. Approach to anisocoria

Reproducedwith permission from: Kedar S, Biousse V, Newman NJ. Approach to the patient with anisocoria. In: UpToDate, Rose, BD (editor), UpToDate, Waltham, MA, 2011. Copyright 2011 UpToDate, Inc. For more information visit www.uptodate.com.

Table 9. Summary of Conditions Causing Anisocoria

	Features	Site of Lesion	Light and Accommodation	Anisocoria	Effect of Pilocarpine
ABNORMAL MIOTIC PUPIL (impaired pupillary dilation)					
Horner's Syndrome	Round, unilateral, ptosis, anhidrosis, pseudoenophthalmos	Sympathetic system	Both brisk	Greater in dark	N/A
Argyll-Robertson Pupil	Irregular, usually bilateral	Midbrain	Poor in light; better to accommodation		N/A
ABNORMAL MYDRIATIC PUPIL (impaired pupillary constriction)					
Adie's Tonic Pupil	Irregular, larger in bright light	Ciliary ganglion	Poor in light, better to accommodation	Greater in light	Constricts (hypersensitivity to dilute pilocarpine)
CN III Palsy	Round	Superficial CN III	± fixed (acutely) at 7-9 mm	Greater in light	Constricts
Pharmacologic Dilation	Round, uni- or bilateral	Iris sphincter	Fixed at 7-8 mm	Greater in light	Will not constrict

Dilated Pupil (Mydriasis)

Sympathetic Stimulation
- fight or flight response
- mydriatic drugs: epinephrine, phenylephrine

Parasympathetic Under-Stimulation
- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes microvascular ischemia (associated with vascular risk factors), vasculitis (e.g. GCA), compression (e.g. pituitary adenoma or posterior communicating artery aneurysm), or midbrain stroke

Acute Angle-Closure Glaucoma
- fixed, mid-dilated pupil

Adie's Tonic Pupil
- 80% unilateral, F>M
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
  - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- long-standing Adie's pupils are smaller than unaffected eye

Trauma
- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit-lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

Constricted Pupil (Miosis)

Senile Miosis
- decreased sympathetic stimulation with age

Parasympathetic Stimulation
- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - opiates, barbiturates

Horner's Syndrome
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis and anhidrosis of ipsilateral face/neck (in pre-ganglionic lesions)
- apraclonidine (strong α-2 and weak α-1 blocker) is the most common pharmacologic diagnostic test, in which denervation hypersensitivity results in dilation of the Horner pupil but not the normal pupil (leading to reversal of anisocoria)

CN III palsy with pupillary involvement may be associated with a posterior communicating artery aneurysm

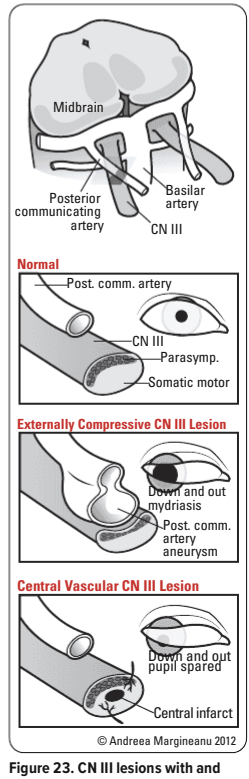


Figure 23. CN III lesions with and without mydriasis

- application of cocaine 4-10% (blocks reuptake of norepinephrine) to eye does not result in dilation of the Horner's pupil, whereas the normal pupil will dilate, thereby confirming the diagnosis
- hydroxyamphetamine 1% (stimulates norepinephrine release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- cocaine and hydroxyamphetamine are rarely used in practice due to issues with availability (cocaine used mainly for children and hydroxyamphetamine is not available in Canada or USA)
- causes: mostly idiopathic but other causes include brainstem infarct (lateral medullary syndrome), Pancoast tumour, neck surgery, and carotid artery dissection
- must rule out carotid artery dissection in acute Horner's syndrome (<14 d old)

Horner's MAP
Miosis
Anhidrosis
Ptosis

Iritis
- miotic pupil initially
- can become irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light

Argyll-Robertson Pupil
- both pupils irregular and <3 mm in diameter, ± ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of neurosyphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)

Relative Afferent Pupillary Defect

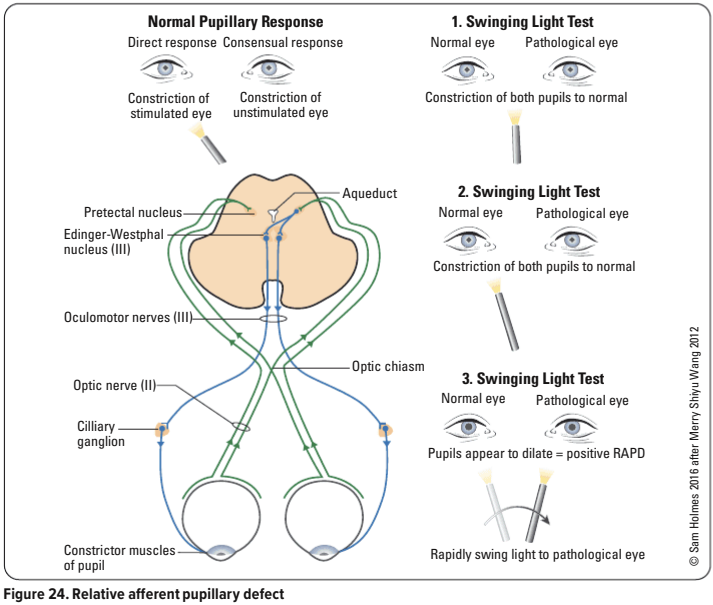


Figure 24. Relative afferent pupillary defect

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light caused by a lesion in visual afferent (sensory) pathway, anterior to optic chiasm
- differential diagnosis: any unilateral or asymmetric optic neuropathy (e.g. optic neuritis, ischemic optic neuropathy, compressive optic neuropathy) or severe retinopathy (e.g. CRAO, large RD, CRVO)
- does not occur with media opacity (e.g. corneal edema, cataracts) or if optic neuropathy is symmetric (since it is relative)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffected eye to the affected eye, "paradoxical" dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides

Cataracts never produce a RAPD

Differentiate RAPD from physiologic pupillary athetosis ("hippus"), which is rapid, rhythmic fluctuations of the pupil, with equal amplitude in both eyes

Malignancies

- uncommon site for 1° malignancies
- see *Retinoblastoma, OP40*

Lid Carcinoma

Etiology
- basal cell carcinoma (90%)
  - spread via local invasion, rarely metastasizes
  - ulcerated centre (rodent ulcer), indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
  - spread via local invasion, may also spread to nodes and metastasize
  - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
  - often masquerades as chronic blepharitis or recurrent chalazion
  - highly invasive, metastasizes
- other: Kaposi's sarcoma, malignant melanoma, Merkel cell carcinoma, metastatic tumour

Treatment
- incisional or excisional biopsies
- may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
- surgical reconstruction

To Find Small Ocular Melanoma

TFSOM
Thickness >2 mm
Subretinal **F**luid
Symptoms – vision changes
Orange pigment
Margin within 3 mm of optic disc

Uveal Melanoma

Etiology
- most common 1° intraocular malignancy in adults
- more prevalent in White individuals
- arise from uveal tract, 90% choroidal melanoma
- hepatic metastases predominate

Clinical Features
- classic appearance of a pigmented dome-shaped mass extending from the ciliary body or the choroid
- diagnosis necessitates expertise of an ophthalmologist/ocular oncologist
- despite treatment, has the possibility of remaining dormant and resurfacing with metastasis years later

Treatment
- investigations: ocular ultrasound, fluorescein angiography, OCT, and systemic cancer investigations
- depending on the size of the tumour, either radiotherapy (brachytherapy vs. external beam) or enucleation
- systemic imaging q3-6 mo for first 5 years after treatment for metastasis to liver recurrence in high risk patients as per molecular testing on diagnosis

Metastases

- most common intraocular malignancy in adults
- most commonly from breast and lung in adults, neuroblastoma in children
- usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
- may present with decreased or distorted vision, irregularly shaped pupil, iritis, and hyphema

Treatment
- local radiation, chemotherapy
- enucleation if blind, painful eye, or large tumour

Ocular Manifestations of Systemic Disease

HIV/AIDS

- up to 75% of patients with AIDS have ocular manifestations

External Ocular Signs
- Kaposi's sarcoma
  - secondary to human herpes virus 8 (HHV-8), causes bright red conjunctival lesion and subconjunctival hemorrhage
  - differential diagnosis: subconjunctival hemorrhage (non-clearing), hemangioma
- multiple molluscum contagiosum
- herpes simplex/zoster keratitis

Retina
- HIV retinopathy (most common)
  - cotton wool spots in >50% of HIV patients
  - intraretinal hemorrhage
- CMV retinitis
  - a necrotizing retinitis, with retinal hemorrhages and vasculitis, "brushfire" or "pizza pie" appearance
  - presents with scotoma (macular involvement and RD), blurred vision, and floaters
  - untreated infection will progress to the other eye in 4-6 wk
  - treatment: virostatic agents (e.g. ganciclovir or foscarnet) via IV, intravitreal injection, or sometimes PO
- necrotizing retinitis
  - from herpes simplex virus, herpes zoster, toxoplasmosis
  - *Pneumocystis carinii* and *Mycobacterium avium intracellulare* can present with choroiditis
  - *Candida* can present as retinitis and vitritis

Other Systemic Infections

- herpes zoster
  - see *Herpes Zoster Ophthalmicus, OP19*
- candidal endophthalmitis
  - fluffy, white-yellow, superficial retinal infiltrates that may eventually result in vitritis
  - may present with inflammation of the anterior chamber
  - treatment: systemic amphotericin B, oral fluconazole, and voriconazole
- toxoplasmosis
  - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous inflammation (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by *Toxoplasma gondii* protozoa transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folinic acid, or clindamycin. Consider adding steroids after if severe inflammation (vitritis, macular, or optic nerve involvement)

Diabetes Mellitus

- most common cause of blindness in working age adults in North America
- loss of vision due to:
  - progressive microangiopathy leading to macular edema
  - progressive DR → neovascularization → traction → RD and vitreous hemorrhage
  - rubeosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

Macular edema is the most common cause of visual loss in patients with background DR

DIABETIC RETINOPATHY

Background
- altered vascular permeability (loss of pericytes and thickening of basement membrane causing breakdown of blood-retinal barrier)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

Clinically significant macular edema is defined as thickening of the retina at or within 500 µm of the centre of the macula

Classification
- non-proliferative: increased vascular permeability and retinal ischemia
  - hard exudates (lipid deposits)
  - dot and blot hemorrhages
  - microaneurysms
  - retinal edema
- advanced non-proliferative (or pre-proliferative)
  - non-proliferative findings plus:
    - intraretinal microvascular abnormalities (IRMA; dilated, non-leaky collateral vessels within retina) in 1 of 4 retinal quadrants
    - retinal hemorrhages ± microvascular anomalies (MAs) (in all 4 retinal quadrants)
    - retinal nerve fibre layer (NFL) infarcts (i.e. cotton-wool spots)
- proliferative
  - 5% of patients with DM will reach this stage
  - neovascularization of iris, disc, and/or retina
    - neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
    - vitreous hemorrhage, bleeding from fragile new vessels, fibrous tissue can contract causing tractional RD
  - may remain asymptomatic in early stage
  - high-risk of severe vision loss secondary to vitreous hemorrhage, RD

Presence of DR in
T1DM
25% after 5 yr
60% after 10 yr
>80% after 15 yr
T2DM
20% at time of diagnosis
60% after 20 yr

Screening Guidelines for Diabetic Retinopathy

- T1DM
  - screen for retinopathy annually beginning 5 yr after disease onset
  - annual screening indicated for all patients over 12 yr and/or entering puberty
- T2DM
  - initial examination at time of diagnosis, then annually
- pregnancy
  - ocular exam in 1st trimester, close follow-up throughout, as pregnancy can exacerbate DR
  - patients with gestational diabetes are not at risk of having DR

Treatment

- 1° prevention: tight control of blood glucose, blood pressure, serum lipid levels, kidney function, and microvascular complications (Diabetic Control and Complications Trial (DCCT))
- 2° prevention: regular screening to monitor for progression
- 3° prevention:
  - pan-retinal laser photocoagulation (PRP) for PDR: reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
  - intravitreal injection of corticosteroids or anti-VEGF for fovea-involved diabetic macular edema
  - macular photocoagulation laser for clinically significant macular edema (when not involving centre of macula)
  - vitrectomy for non-clearing vitreous hemorrhage ± tractional RD in PDR
    - vitrectomy before vitreous hemorrhage does not improve the visual prognosis

LENS CHANGES

- earlier onset of senile nuclear sclerotic and cortical cataracts
- may get hyperglycemic cataract due to sorbitol accumulation (rare)
- changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3-4 diopters due to induced osmotic changes of the lens

EXTRAOCULAR MUSCLE PALSY

- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- may involve CN IV and VI
- usually recover within a few months

OPTIC NEUROPATHY

- VA loss due to infarction of optic disc/nerve

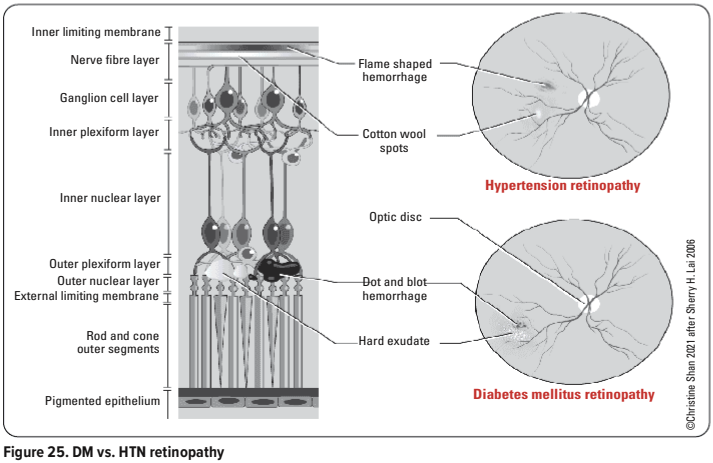


Figure 25. DM vs. HTN retinopathy

Hypertension

- retinopathy is the most common ocular manifestation
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema
- chronic HTN retinopathy: arteriovenous (AV) nicking, flame/dot/blot retinal hemorrhages, cotton wool spots
- increases risk for many other ocular diseases (DR, BRVO, CRAO/BRAO)

Anti-Vascular Endothelial Growth Factor for Diabetic Macular Oedema: A Network Meta-Analysis
Cochrane DB Syst Rev 2018;10:CD007419
Purpose: To compare the effectiveness and safety of the different anti-VEGF drugs using network meta-analysis methods.
Results: Included 24 studies with 6007 patients with diabetic macular edema (DME) and moderate vision loss. Aflibercept, bevacizumab, and ranibizumab were all more effective than laser therapy for improving vision by 3 or more lines after one yr. Aflibercept may confer some advantage over ranibizumab and bevacizumab. There were no differences in adverse events.
Conclusions: Anti-VEGF drugs are effective at improving vision in people with DME with three to four in every 10 people likely to experience an improvement of 3 or more lines VA at one yr. More evidence on the long-term (greater than two yr) comparative effects of these anti-VEGF agents is needed.

Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: 2 Year Result from a Comparative Effectiveness Randomized Clinical Trial
Ophthalmology 2016;123:1351-1359
All 3 anti-VEGF agents showed improvement of VA and decreased number of injections in yr 2. Among eyes with worse baseline VA, aflibercept had superior 2 yr VA compared with bevacizumab, but superiority over ranibizumab in yr 1 was no longer identified.

Effects of Medical Therapies on Retinopathy Progression in T2DM
NEJM 2010;363:233-244
See Landmark Ophthalmology Trials table for more information on Effects of Medical Therapies on Retinopathy Progression in T2DM, which details whether intensive glycemic control, combination therapy for dyslipidemia, and intensive blood pressure control can limit the progression of DR.

Table 10. Modified Scheie Classification

Classification	
Grade 0	No changes
Grade 1	Mild arterial narrowing
Grade 2	Obvious arterial narrowing with focal irregularities
Grade 3	Grade 2 + retinal hemorrhages and/or exudate
Grade 4	Grade 3 + swollen optic nerve (malignant HTN)

Multiple Sclerosis

- see Neurology, N55

Clinical Features
- blurred vision and decreased colour vision secondary to optic neuritis
- central scotoma due to damage to papillomacular bundle of retinal nerve fibres
- diplopia secondary to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

Treatment
- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation due to increased risk of developing MS

Corticosteroids for Treating Optic Neuritis
Cochrane DB Syst Rev 2015;8:CD001430
Summary: No conclusive evidence of benefit in terms of recovery to normal VA, visual field, or contrast sensitivity six mo after initiation of IV or oral corticosteroids.
Results: After review of 6 RCTs evaluating systemic corticosteroids for treatment of acute optic neuritis, all meta-analyses show similar outcomes for placebo vs. corticosteroid group for VA, contrast sensitivity, and visual field.

Transient Ischemic Attack/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles) sometimes seen

Graves' Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur mainly due to increased fibroblast proliferation and accumulation of hydrophilic glycosaminoglycans (mostly hyaluronic acid) in the extraocular muscles and orbital tissues

The most common cause of unilateral or bilateral proptosis in adults is Graves' disease

Clinical
- initial inflammatory phase is followed by a quiescent cicatricial phase

Treatment
- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, proptosis, and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides

Progression of Signs and Symptoms of Graves' Ophthalmopathy

NO SPECS
No signs/symptoms
Only signs (lid retraction, lid lag)
Soft tissue swelling (periorbital edema)
Proptosis (exophthalmos)
Extraocular muscle weakness (causing diplopia)
Corneal exposure
Sight loss

Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjögren's syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)

Giant Cell Arteritis/Temporal Arteritis

- see Rheumatology, RH22

Clinical Features
- more common in women >60 yr
- sudden loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and PMHx of polymyalgia rheumatica
- ischemic optic neuropathy or, less commonly, CRAO often preceded by transient monocular vision loss
- very high risk of vision loss in contralateral eye if untreated

ESR in GCA/Temporal Arteritis
Males >age/2
Females >(age + 10)/2

Diagnosis
- CBC (thrombocytosis), elevated ESR and CRP
- temporal artery biopsy

Treatment
- high dose corticosteroids to prevent further ischemic complications and improve systemic symptoms
- if diagnosis of GCA is suspected clinically: start STAT treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation

Sarcoidosis

Clinical Features
- granulomatous uveitis with large "mutton fat" keratic precipitates and posterior synechiae
- complications include glaucoma, cataracts, retinal hemorrhages, peripheral retinal neovascularization, and dry eye
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

Treatment
- topical/systemic steroids and mydriatics

Pediatric Ophthalmology

Strabismus

Strabismus in children under 4 mo of age sometimes resolves, particularly if the deviation is intermittent, variable, or measures <40 prism diopters

All children with strabismus and/or possible reduced vision require prompt referral to an ophthalmologist

- ocular misalignment in one or both eyes, can be found in up to 3% of children
- classification
  - manifest (constant) vs. latent (hidden) alignment
  - comitant (deviation equal in all positions of gaze) vs. incomitant (deviation worse in certain positions, may be paralytic or restrictive)
  - described in direction of deviation relative to the fixating eye
- distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism)
- complications: amblyopia, interferes with social interactions

Heterotropia
- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

Heterophoria
- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue, illness, inattention)

Types
- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = "crossed-eyes"; exotropia = "wall-eyed"

Tests
- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle κ)
  - positive in -tropias; negative in -phorias
- cover-uncover test allows to differentiate between -tropias and -phorias
  - any movement of the non-occluded eye in a single cover test indicates a -tropia, as that eye picks up fixation in the absence of visual input to the dominant eye
  - any movement of the occluded eye in a cover-uncover test indicates a -phoria
- alternate cover test
  - alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - maintain cover over one eye for 2-3 s before rapidly shifting to other eye
  - deviation can be quantified using a prism over one eye (alternate prism cover test)

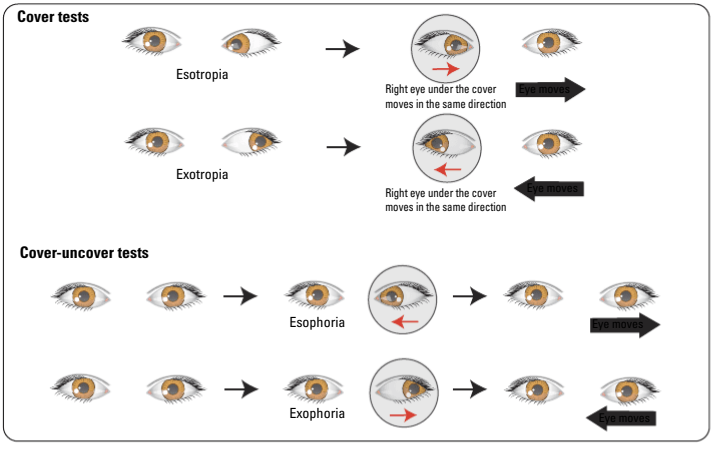


Figure 26. Cover and cover-uncover tests for detection of tropia and phoria

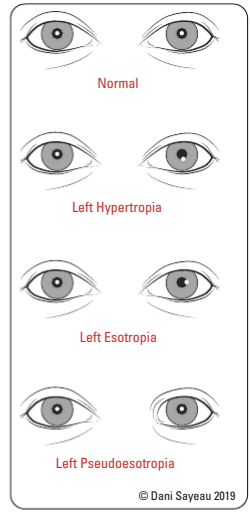


Figure 27. Hirschberg test

Table 11. Paralytic vs. Non-Paralytic Strabismus

Clinical Characteristics	Paralytic Strabismus	Non-Paralytic Strabismus
Definition	Incomitant strabismus	Concomitant strabismus
Onset	Acute onset, but may be gradual or congenital	Usually gradual or shortly after birth; rarely acute
Age of Onset	Any age; most often acquired	Usually during infancy
Etiology	Reduction or restriction in range of eye movements due to: Neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumour, trauma Muscular: myasthenia gravis (neuromuscular junction pathology), Graves' disease Structural: restriction or entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall	Develops early in childhood No restriction in range of eye movements Monocular, alternating, or intermittent
Diplopia	Common	Uncommon; image from the misaligned eye is suppressed
Visual Acuity in Other Eye	Usually unaffected in the other eye, unless CN II is involved	Deviated eye may become amblyopic if not treated when the child is young Amblyopia treatment rarely successful after age 8-10 yr Amblyopia usually does not develop if child has alternating strabismus or intermittency, which allows neural pathways for both eyes to develop
Possibility of Amblyopia	Uncommon	Common
Neurologic Findings or Systemic Disease	May be present	Usually absent

Accommodative Esotropia

- triad of the near reflex (i.e. convergence, accommodation, miosis) represents normal response to approaching object
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 yr
- reversible with correction of refractive error
- partially accommodative esotropia refers to partial resolution of esotropia following correction of refractive error

Non-Accommodative Esotropia

- accounts for 50% of childhood strabismus
- most are idiopathic
- congenital (or infantile) esotropia is a common and important subtype
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

Exotropia
- accounts for 11-18% of childhood strabismus
- congenital: onset before 6 mo, may be associated with other conditions (e.g. neurologic, craniofacial disorders)
- acquired
  - intermittent exotropia: typically apparent when patient is tired, sick, or looking in the distance
  - consecutive exotropia: develops after strabismus surgery

Amblyopia

Definition
- neurodevelopmental visual disorder with unilateral or bilateral (less common) reduction of BCVA that cannot be attributed only to the effect of an ocular structural abnormality
- most common cause of vision loss in children
- cannot be remedied immediately by prescription eyewear alone

Etiology
- progressive suppression of visual input from eye receiving suboptimal image (blurry from uncorrected refractive error, deviated)
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia)
- other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors, usually in the eye with higher refractive error), and deprivation due to structural ocular problems (ptosis, cataract, corneal opacity/scarring, retinoblastoma)

Diagnosis
- "Holler Test": young child upset if good eye is covered
- quantitative VA by age 3-4 yr using picture charts and/or matching game (Sheridan-Gardiner), LEA symbols, testing each eye separately

Management
- strabismus
  - correct with glasses for accommodative esotropia
  - occlusion therapy (see below)
  - surgery: recession (weakening) by moving muscle insertion further back on the globe or resection (strengthening) by shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until ~8 yr of age
  - no proven value for vision therapy/training in the treatment of strabismus or amblyopia
- anisometropia
  - the eye with the lower refractive error receives a clear image, while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if VA difference persists after using glasses for 4-8 wk
- deprivation: treat underlying cause
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
  - prognosis: 90% of strabismic/anisometropic amblyopia will have good vision restored and maintained if treated before age 4 yr, but deprivational has a worse prognosis

Amblyopia Therapy
- occlusion: full or part-time patching of the good eye to force the brain to use the non-dominant eye and redevelop its vision with follow-up to prevent occlusion amblyopia
- cycloplegic drops (e.g. atropine) to impair accommodation and blur vision in the good eye

Risks
- permanent loss of vision in the affected eye
- reverse amblyopia: over-treatment with either occlusion or atropine penalization in the better-seeing eye
- safety glasses or polycarbonate lenses recommended if VA in worse eye is <20/50 to reduce risk of traumatic injury to the better-seeing eye
- loss of stereopsis

Leukocoria

Definition
- white pupillary reflex (red reflex is absent)
- the presence of leukocoria warrants urgent referral to an ophthalmologist

Differential Diagnosis
- retinoblastoma
- cataract
- Coats disease (exudative retinal telangiectasis)
- persistent hyperplastic primary vitreous or persistent fetal vasculature
- combined hamartoma of retina and RPE
- retinal coloboma (chorioretinal)
- RD
- congenital infections (e.g. toxoplasmosis and toxocariasis)
- ROP

Retinoblastoma

Definition
- intraocular malignancy that rapidly develops from immature cells of the retina

Epidemiology
- most common primary intraocular malignancy in children
- incidence: 1/15000
- unilateral (2/3) or bilateral (1/3)
- malignant – direct or hematogenous spread

Etiology
- sporadic or genetic transmission; screening of siblings/children is essential
- inherited forms likely to be bilateral
- most commonly associated with *RB1* inactivation (tumor suppressor gene); may also be associated with MYCN amplification (oncogene) in rare cases

Diagnosis
- often presents with leukocoria and/or strabismus
- other signs: red eye, eye enlargement if advanced disease
- fundus examination (nodular, white/cream-coloured masses with intralesional blood vessels)
- U/S (A & B-scan) or MRI may demonstrate RD and/or calcified mass (present in most cases)

Treatment
- local (laser, cryotherapy, chemotherapy), systemic chemotherapy, and/or enucleation + genetic counselling

Retinal Zones
- Zone I: circle centred at the nerve with radius twice the distance from the disc to the macula (most difficult to treat)
- Zone II: annulus from zone I to nasal extent of retina (nasal ora serrata)
- Zone III: remaining retina

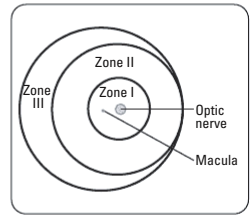


Figure 28. Zones of the retina in ROP

Retinopathy of Prematurity

Definition
- vasoproliferative retinopathy that is a major cause of childhood blindness in low- and middle-income countries

Risk Factors
- non-Black race (Black infants have lower risk of developing ROP)
- earlier gestational age, low birth weight (i.e. <1500 g), low caloric intake, postnatal hyperglycemia
- high oxygen exposure after birth (iatrogenic), i.e. assisted ventilation >1 wk

Classification (ROP Staging)
- stage 1: flat white demarcation line at the junction between the vascular and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial RD (4A: macula "on", 4B: macula "off")
- stage 5: total RD
- plus (+) disease: dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with circumferential extent of ROP involvement in 5 continuous or 8 cumulative clock hours

Treatment
- laser ablation is currently the treatment standard for stages 3+; intravitreal bevacizumab and ranibizumab both showed significant benefits in zone I compared to laser ablation therapy in infants with stage 3+ ROP
- stage 4-5 is treated with vitrectomy/scleral buckle (goal is to release vitreous tractional forces on the retina)

Anti-VEGF Drugs for Treatment of Retinopathy of Prematurity (ROP)
Cochrane DB Syst Rev 2018;1:CD009734
Summary/Conclusions: Review of 6 RCTs/Quasi-RCTs comparing anti-VEGF agents vs. conventional therapy for ROP (n=383).
- Insufficient data precludes strong conclusions for routine use of intravitreal anti-VEGF agents for treatment of ROP
- Intravitreal bevacizumab/ranibizumab as monotherapy reduces risk of refractive errors during childhood
- Intravitreal pegaptanib + laser therapy reduces the risk of retinal detachment for type 1 ROP
- Effect on other critical outcomes and long-term systemic adverse effects are unknown

Prognosis
- higher incidence of myopia among ROP infants, even if treated successfully (less refractive error among anti-VEGF treated vs. laser treated)
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

Nasolacrimal System Defects

Definition
- congenital obstruction of the nasolacrimal duct (failure of canalization) at valve of Hasner, ~1-2 mo of age

Signs and Symptoms
- epiphora (overflow of tears), periocular crusting, mucopurulent discharge, recurrent conjunctivitis
- pressure over the lacrimal sac may cause reflux of mucopurulent material from lacrimal punctum

Treatment
- Crigler massage over lacrimal sac at medial canthus
- vast majority spontaneously resolve by 1 yr of age, otherwise consider referral for duct probing

Ophthalmia Neonatorum

Definition
- purulent conjunctivitis with profuse exudate in the first few days of life; can cause blindness

Gonococcal infection is the most serious threat to sight as it can rapidly penetrate corneal epithelium, causing corneal ulceration

Etiology
- chemical/toxic: silver nitrate (occurs in first 24 h), erythromycin (secondary to prophylaxis, self-limiting)
- infectious: bacterial (e.g. *N. gonorrhoeae* – most common, occurs at around 3-4 d of life; *C. trachomatis* – occurs at around 7 d of life), herpes simplex virus – occurs at approximately 2 wk of life

Treatment
- systemic antibiotics and saline irrigation with possible hospitalization if infectious etiology

Congenital Glaucoma

Epiphora in children – rule out congenital glaucoma

Definition
- elevated IOP within the first year of life

Etiology
- not entirely known – may be due to inadequate development of anterior chamber
- sporadic and hereditary (autosomal recessive); males more often affected
- secondary congenital glaucoma can be associated with ocular and systemic disorders
  - ocular: aniridia, microcornea, megalocornea, microphthalmos, persistent hyperplastic primary vitreous, Sturge-Weber syndrome, Axenfeld-Rieger syndrome, neurofibromatosis
  - systemic: Prader-Willi, trisomies, fetal alcohol syndrome, mucopolysaccharidoses, and many others

Clinical Features
- photophobia, epiphora, and blepharospasm
- cloudy cornea due to edema; Haab's striae due to breaks in Descemet's membrane
- increased IOP, rapidly-progressive myopia
- buphthalmos (large cornea, "ox eye") and enlarged CDR

Treatment
- immediate angle surgery after diagnosis

Ocular Trauma

Blunt Trauma

- caused by blunt object such as fist
- HPI: injury, ocular history, drug allergy, tetanus status
- PEx: VA first, pupil size and reaction, EOM (diplopia), external and slit-lamp exam, fundoscopy
  - if VA normal or slightly reduced: globe less likely to be perforated
  - if VA reduced: possible globe perforation, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema (air) of lid

Always test VA first – medicolegal protection

- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion (detect with fluorescein staining and cobalt blue filter using slit-lamp or ophthalmoscope)
- anterior chamber: assess depth, presence of cells, hyphema, hypopyon
- iris: iridodialysis, prolapse, iritis
- lens: cataract, dislocation
- vitreous: hemorrhage
- retina: tear, detachment

Penetrating Trauma

- includes: ruptured globe ± lid laceration, prolapsed iris, intraocular foreign body
- rule out intraocular foreign body with CT orbit, especially if history of "metal striking metal"
- **OCULAR EMERGENCY**: initial management - **REFER IMMEDIATELY**
  - ABCs
  - avoid pressing on eye globe
  - avoid checking IOP
  - check vision, diplopia
  - apply rigid eye shield to protect from further trauma
  - keep head elevated 30-45° to keep IOP down
  - keep NPO
  - check tetanus status
  - give IV antibiotics
    - selecting appropriate agents depends on the mechanism of injury; Gram-positive bacteria are more commonly involved than Gram-negative; retained intraocular foreign objects increase the risk of infections with Bacillus species, whereas exposure to vegetable matter increase the risk of a fungal etiology

Hyphema

Definition
- blood in anterior chamber, often due to damage to root of the iris
- may occur with blunt trauma

Treatment
- refer to ophthalmology
- shield and bedrest/minimal exertion for 5 d or as determined by ophthalmologist
- sleep with head of bed elevated
- may require surgical drainage if hyphema persists or if re-bleed

Complications
- risk of re-bleed highest on day 2-5, and may result in secondary glaucoma, corneal staining, and iris necrosis
- never prescribe acetylsalicylic acid (increases risk of re-bleed)

Blow-Out Fracture

• see Plastic Surgery, PL34

Definition
• blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
• orbital rim remains intact
• inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
• infraorbital nerve courses along the floor of the orbit and may be damaged

Clinical Features
• pain and nausea at time of injury
• diplopia, restriction of EOM
• infraorbital and upper lip paresthesia or anesthesia (CN V2)
• enophthalmos (sunken eye) and periorbital ecchymosis

Investigations
• CT: anteroposterior and coronal view of orbits

Treatment
• avoid coughing, blowing nose, and Valsalva maneuvers
• systemic antibiotics may be indicated
• surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
• may delay surgery if the diplopia improves

Refer if You Observe Any of These Signs
- Decreased VA
- Shallow anterior chamber
- Hyphema
- Abnormal pupil
- Ocular misalignment
- Retinal damage

Management of Suspected Globe Rupture

CAN'T forget
CT orbits
Ancef (cefazolin) ± aminoglycoside IV
NPO
Tetanus status

Post-Traumatic Infectious Endophthalmitis
Surv Ophthalmol 2011;56:214-251
- Delayed primary repair (>24 h after open globe injury) increases risk for post-traumatic endophthalmitis in the absence of an intraocular foreign body (IOFB)
- If IOFB present, early vitrectomy and IOFB removal must be performed within 24 h of injury
- Extreme pain with hypopyon and vitritis indicate endophthalmitis until proven otherwise, and samples must be obtained for culture
- Treat with empirical intravitreal and intravenous antibiotic guided by nature of trauma, and adjust based on culture

Shaken Baby Syndrome
Syndrome of findings characterized by absence of external signs of abuse with respiratory arrest, seizures, or coma. Ocular exam findings are important diagnostically for Shaken Baby Syndrome. These findings include extensive retinal and vitreous hemorrhages that occur during the shaking process and are extremely rare in accidental trauma. A detailed fundoscopic exam or an ophthalmology referral should be conducted for all infants in whom abuse is suspected.

Classic Signs of Blow-Out Fracture
- Enophthalmos
- Decreased upgaze (inferior rectus trapped)
- Cheek anesthetized (infraorbital nerve trapped)

Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks – thus, very guarded prognosis

Treatment

- immediately irrigate with water or balanced saline solution (BSS)
  - irrigate with eyelids retracted in emergency department with IV drip to physiologic pH (test with litmus paper)
  - swab upper and lower fornices to remove possible particulate matter
- do not attempt to neutralize an acid with a base, or vice versa
- topical antibiotics and patching
- topical cycloplegics to decrease iris spasm (pain) and prevent secondary glaucoma (due to posterior synechiae formation)
- topical steroids (prescribed by ophthalmologist) to decrease inflammation, use for <2 wk in the case of a persistent epithelial defect

Ocular Drug Toxicity

Table 12. Drugs with Ocular Toxicity

Drugs	
Amiodarone	Corneal microdeposits and superficial keratopathy (vortex keratopathy) Rare: ischemic optic neuropathy
Atropine, benztropine	Pupillary dilation (risk of angle-closure glaucoma)
Bisphosphonates (Fosamax®, Actonel®)	Inflammatory eye disease (iritis, scleritis, episcleritis)
Chloroquine, hydroxychloroquine	Bull's eye maculopathy Vortex keratopathy
Chlorpromazine	Anterior subcapsular cataract
Contraceptive pills	Decreased tolerance to contact lenses Migraine Retinal vein occlusion
Digitalis	Yellow vision Blurred vision
Ethambutol	Optic neuropathy
Haloperidol (Haldol®)	Oculogyric crises Blurred vision
Indomethacin	Superficial keratopathy
Interferon	Retinal hemorrhages and cotton wool spots
Isoniazid	Optic neuropathy
Nalidixic acid	Papilledema
Steroids	Posterior subcapsular cataract Glaucoma Increased severity of HSV infections (geographic ulcers) Predisposition to fungal infections
Sulfonamides, NSAIDs	Stevens-Johnson syndrome
Tamsulosin (Flomax®)	Intraoperative floppy iris syndrome (can complicate cataract surgery)
Tetracycline	Papilledema
Thioridazine	Pigmentary degeneration of retina
Vigabatrin	Retinal deposition with macular sparing, peripheral visual field loss
Vitamin A toxicity	Papilledema
Vitamin D toxicity	Band keratopathy

Common Medications

TOPICAL OCULAR DIAGNOSTIC DRUGS

Fluorescein Dye
- water-soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope, slit-lamp ± applanation tonometry)
- absorbed in areas of epithelial loss (ulcer, abrasion, laceration)
- stains mucus, contact lenses, foreign bodies

Rose Bengal Stain
- stains devitalized epithelial cells and mucus to indicate tear film abnormalities (e.g. mucin deficiency)

Anesthetics
- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, and examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore NEVER prescribe

Mydriatics
- dilate pupils
- two classes
  - cholinergic blocking (e.g. tropicamide – Mydriacyl®)
    - dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    - indications: refraction, fundoscopy, therapy for iritis
  - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    - stimulate pupillary dilator muscles, no effect on accommodation
    - usually used with tropicamide for additive effects
    - side effects: HTN, tachycardia, arrhythmias

Table 13. Mydriatic Cycloplegic Drugs and Duration of Action

Drugs	Duration of Action
Tropicamide (Mydriacyl®) 0.5%, 1%	4-5 h
Cyclopentolate HCl 0.5%, 1%	3-6 h
Homatropine HBr 1%, 2%	3-7 d
Atropine sulfate 0.5%, 1%	1-2 wk
Scopolamine HBr 0.25%, 5%	1-2 wk

GLAUCOMA MEDICATIONS

Table 14. Glaucoma Medications

Drug Category	Dose	Effect	Comment/Side Effects
α-Agonist **α2-selective** • brimonidine 0.2% (Alphagan®) • apraclonidine 0.5% (Iopidine®)	1 gtt OS/OD BID/TID	Non-selective: reduced aqueous production + increased TM outflow Selective: reduced aqueous production + increased uveoscleral outflow	Non-selective: mydriasis, macular edema, tachycardia Selective: contact allergy, hypotension/apnea in children
β-Blocker Non-selective • timolol (Timoptic®) • levobunolol (Betagan®) **β 1-selective** • betaxolol (Betoptic®)	1 gtt OS/OD once daily/BID	Reduced aqueous production	**Bronchospasm (caution in asthma/COPD)** Increased CHF Bradycardia, hypotension, depression, heart block, impotence
Carbonic Anhydrase Inhibitor • dorzolamide (Trusopt®) • brinzolamide (Azopt®) • oral: acetazolamide (Diamox®), methazolamide (Neptazane®)	1 gtt OS/OD TID Diamox®: 500 mg PO BID	Reduced aqueous production	**Must ask about sulfa allergy** Generally local side effects with topical preparations Oral: diuresis, fatigue, paresthesia, GI upset
Parasympathomimetic (cholinergic stimulating) • pilocarpine (Pilopine®) • carbachol (Isopto Carbachol®)	1-2 gtts OS/OD TID/QID	Increased TM outflow	Miosis Reduced night vision Increased GI motility, brow ache, headache Reduced heart rate
Prostaglandin Analogues • latanoprost (Xalatan®) • travaprost (Travatan®) • bimatoprost (Lumigan®)	1 gtt OS/OD QHS	Increased uveoscleral outflow (uveoscleral responsible for 20% of drainage)	Iris colour change Periorbital skin pigmentation Lash growth Conjunctival hyperemia

Cosopt® = timolol + dorzolamide; Xalacom® = timolol + lantanoprost; Combigan® = timolol + brimonidine; DuoTrav® = timolol + travaprost; gtt = drop, gtts = drops

Ophthalmic Drop Cap Colours

Green	Cholinergics
Red	Anticholinergics
White	Anesthetics, antibiotics, artificial tears, steroids
Yellow	β-blockers
Blue	β-blocker combinations
Purple	α-agonists
Teal	Prostaglandins
Orange	Carbonic anhydrase inhibitors
Tan	Fluoroquinolones
Grey	NSAIDs
Pink	Anti-inflammatories, steroids

WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

VEGF Inhibitors (Anti-VEGF)

- anti-VEGF agents control ocular angiogenesis to prevent development of choroidal neovascularization and reduce abnormal vascular permeability
- administered via intravitreal injections
- aflibercept (Eylea®) is a VEGF "trap" agent that binds VEGF-A, B, and placental growth factor
- ranibizumab (Lucentis®) is a monoclonal Fab fragment and non-selective anti-VEGF agent
- brolucizumab (Beovu®) is a humanized monoclonal single-chain variable fragment antibody directed against human VEGF-A
- faricimab (Vabysmo®) is a bispecific antibody that acts by neutralizing both VEGF-A and Ang-2 proteins, a dual mode of action
- bevacizumab (Avastin®) is recombinant humanized monoclonal IgG antibody and non-selective anti-VEGF agent
  - FDA-approved only for treatment of metastatic breast cancer, colorectal cancer, and non-small cell lung cancer; therefore, its widespread ophthalmologic use is off-label

Intravitreal Bevacizumab vs. Ranibizumab for Treatment of Neovascular Age-Related Macular Degeneration: Findings from a Cochrane Systematic Review
Ophthalmology 2016; 123(1):70-77
Summary: In 6 RCTs with 2809 participants, there were no important differences in effectiveness or safety between bevacizumab and ranibizumab, despite a significant cost difference.

Antiplatelet and Anticoagulant Drugs Do Not Affect Visual Outcome in Neovascular Age-Related Macular Degeneration in the BRAMD Trial
Am J Ophthalmol 2018;187:130-137
Summary: In 330 NVAMD patients receiving either bevacizumab or ranibizumab treatment, use of anti-coagulant and anti-platelet agents was not associated with visual decline or occurrence of ocular hemorrhages.

TOPICAL OCULAR THERAPEUTIC DRUGS

NSAIDs

- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

Anti-Histamines

- used to relieve red and itchy eyes, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes
- olopatadine (Patanol®, Pataday®)

Decongestants

- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine (Isopto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle-closure glaucoma

Antibiotics

- indications: bacterial and hyperpurulent conjunctivitis, corneal abrasions and ulcers, endophthalmitis, keratitis, blepharitis, globe rupture, cellulitis, lacrimal sac, and lacrimal gland infections
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), aminoglycosides (gentamicin (Garamycin®), tobramycin (Tobrex®)), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (ciprofloxacin (Ciloxan®), ofloxacin (Ocuflox®), moxifloxacin (Vigamox®), gatifloxacin (Zymar®))

Corticosteroids

- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®), loteprednol etabonate 0.5% (Lotamax®), and difluprednate (Durezol®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  - potentiates HSV keratitis and fungal keratitis as well as masking symptoms
  - increased IOP, more rapidly in steroid responders (within weeks)
  - posterior subcapsular cataract (within months)

Landmark Ophthalmology Trials

Trial Name	Reference	Clinical Trial Details
AGE-RELATED MACULAR DEGENERATION		
AREDS2	JAMA 2013;309(19):2005-2015	**Title**: Lutein + Zeaxanthin and Omega-3 Fatty Acids for AMD: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial **Purpose**: Purpose: To determine whether adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation (vitamins C and E, β-carotene, zinc, and copper) decreases the risk of developing advanced AMD and to evaluate the effect of eliminating β-carotene, lowering zinc doses, or both in the AREDS formulation. **Methods**: Patients at risk for progression to advanced AMD were randomized to receive lutein + zeaxanthin, DHA + EPA, lutein + zeaxanthin and DHA + EPA, or placebo, in addition to taking the AREDS formula. **Results**: Comparison with placebo (AREDS formula alone) in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD. There was no apparent effect of β-carotene elimination or lower-dose zinc on progression to advanced AMD. More lung cancers were noted in the β-carotene, mostly in former smokers. **Conclusions**: Addition of lutein+zeaxanthin, DHA+EPA, or both to the AREDS formulation did not further reduce risk of progression to advanced AMD. Because of the potential increased incidence of lung cancer with high doses of β-carotene, lutein+zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.
CATT	NEJM 2011;364(20):1897-908	**Title**: Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration **Purpose**: To assess the efficacy and safety of ranibizumab and bevacizumab and to determine whether an as-needed regimen would compromise long-term VA, as compared with a monthly regimen. **Methods**: Patients with neovascular AMD were randomized to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in VA at 1 yr. **Results**: Bevacizumab was equivalent to ranibizumab whether it was administered monthly or as needed. Ranibizumab as needed was equivalent to monthly ranibizumab, but the comparison of bevacizumab as needed and monthly was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group than in the other groups. The rates of death, myocardial infarction, and stroke were not statistically different. **Conclusions**: Bevacizumab and ranibizumab had equivalent effects on VA at 1 yr when administered according to the same schedule. There was no difference between ranibizumab given as needed and ranibizumab given monthly.
GLAUCOMA		
OHTS	Arch Ophthalmol 2002;120(6):701-13	**Title**: The Ocular Hypertension Treatment Study: A Randomized Trial Determines That Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma **Purpose**: To determine the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of POAG. **Methods**: 1636 patients with no evidence of glaucomatous damage and with IOP between 24-32 mmHg in one eye and between 21-32 mmHg in the other eye were randomized to observation or to treatment with commercially available topical ocular hypotensive medication. The primary outcome was development of visual field abnormality or optic disc deterioration attributed to POAG. **Results**: Mean reduction in IOP in the medication group was 22.5%±9.9% vs. 4.0%±11.6% in the observation group. At 5 years, the probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group (P<0.0001). **Conclusions**: Topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP.
UKGTS	Lancet 2015;385(9975):1295-304	**Title**: Latanoprost for Open-Angle Glaucoma (UKGTS): A Randomised, Multicentre, Placebo-Controlled Trial **Purpose**: To assess vision preservation in patients given latanoprost compared with those given placebo. **Methods**: Patients with newly diagnosed POAG were randomized to receive either latanoprost 0.005% or placebo eye drops. The primary outcome was time to visual field deterioration within 24 months. **Results**: At 24 months, mean reduction in IOP was 3.8 mmHg in 231 patients assessed in the latanoprost group and 0.9 mmHg in 230 patients assessed in the placebo group. Visual field preservation was significantly longer in the latanoprost group than in the placebo group. **Conclusions**: There is preservation of the visual field with an intraocular-pressure-lowering drug, latanoprost, in patients with POAG.
DIABETIC RETINOPATHY		
Effects of Medical Therapies on Retinopathy Progression in T2DM	NEJM 2010;363:233-244	**Title**: Effects of Medical Therapies on Retinopathy Progression in T2DM **Purpose**: To determine whether intensive glycemic control, combination therapy for dyslipidemia, and intensive blood pressure control can limit the progression of DR in persons with T2DM. **Methods**: Participants with T2DM at high-risk of cardiovascular disease were randomized to receive either intensive or standard treatment for glycemia, dyslipidemia, or systolic blood-pressure control. Participants were evaluated for the effect of these interventions on the progression of DR. **Results**: Rates of progression of DR at 4 yr were 7.3% with intensive glycemia treatment vs. 10.4% with standard therapy; 6.5% with fenofibrate for intensive dyslipidemia therapy vs. 10.2% with placebo and 10.4% with intensive blood pressure therapy vs. 8.8% with standard therapy. **Conclusions**: Intensive glycemic control and intensive combination treatment of dyslipidemia, but not intensive blood pressure control, reduced the rate of DR.
UKPDS 69	Arch Ophthalmol 2004;122(11):1631-40	**Title**: Risks of Progression of Retinopathy and Vision Loss Related to Tight Blood Pressure Control in Type 2 Diabetes Mellitus: UKPDS 69 **Purpose**: To determine the relationship between tight BP control and the different aspects of DR in patients with T2DM. **Methods**: 758 patients were allocated to a tight BP control policy (<150/85) with angiotensin-converting enzyme inhibitor or β-blockers as the main therapy; 390 were allocated to a less tight BP control policy (<180/105). **Results**: There was a significantly higher microaneurysm count, hard exudates prevalence, and cotton-wool spots in the tight BP control group compared to the less tight BP control group. Patients with tight BP control were less likely to undergo photocoagulation. The cumulative incidence of the end point of blindness in 1 eye was 18/758 for the tight BP control group compared with 12/390 for the less tight BP control group. **Conclusions**: High BP is detrimental to each aspect of diabetic retinopathy; a tight BP control policy reduces the risk of clinical complications from diabetic eye disease.

Trial Name	Reference	Clinical Trial Details
EDTRS 9	Ophthalmology 1991;98:766-85	**Title**: Early Photocoagulation for Diabetic Retinopathy. ETDRS Report Number 9. Early Treatment Diabetic Retinopathy Study Research Group **Purpose**: To evaluate the efficacy of argon laser photocoagulation in deterring the progression of early DR into more advanced DR, as well as best time to initiate treatment. **Methods**: For patients with mild-to-severe non-proliferative or early proliferative DR in both eyes, one eye of each patient was assigned randomly to early photocoagulation and the other to deferral of photocoagulation (initiated as soon as high-risk proliferative retinopathy was detected). Eyes selected for early photocoagulation received one of four different combinations of scatter and focal treatment. **Results**: Early treatment was associated with a small reduction in the incidence of severe visual loss compared with deferral of photocoagulation, but 5-year rates were low in both the early treatment and deferral groups (2.6% and 3.7%). Adverse effects of scatter photocoagulation on visual acuity and visual field also were observed. **Conclusions**: Scatter photocoagulation is not recommended for eyes with mild or moderate nonproliferative diabetic retinopathy but is for more severe disease and should not be delayed. Focal photocoagulation is recommended for eyes with macular edema, as it reduces the risk of visual loss.
NEUROPHTHALMOLOGY		
Optic Neuritis Treatment trial	NEJM 1992; 326(9):581-8	**Title**: A Randomized, Controlled Trial of Corticosteroids in the Treatment of Acute Optic Neuritis **Purpose**: To evaluate corticosteroids as treatment for optic neuritis. **Methods**: Patients with acute optic neuritis were randomly assigned oral prednisone, intravenous methylprednisolone followed by oral prednisone, or oral placebo. Visual function was assessed over a six-month follow-up period. **Results**: Visual function recovered faster in the group receiving intravenous methylprednisolone than in the placebo group; this was particularly true for the reversal of visual-field defects. The outcome in the oral-prednisone group did not differ from that in the placebo group. In addition, the rate of new episodes of optic neuritis in either eye was higher in the group receiving oral prednisone, but not the group receiving intravenous methylprednisolone, than in the placebo group. **Conclusions**: Intravenous methylprednisolone followed by oral prednisone speeds the recovery of visual loss due to optic neuritis and results in slightly better vision at six months. Oral prednisone alone, as prescribed in this study, is an ineffective treatment and increases the risk of new episodes of optic neuritis.
Idiopathic Intracranial Hypertension Treatment Trial	JAMA. 2014;311(16):1641-1651	**Title**: Effect of Acetazolamide on Visual Function in Patients With Idiopathic Intracranial Hypertension and Mild Visual Loss **Purpose**: To determine whether acetazolamide is beneficial in improving vision when added to a low-sodium weight reduction diet in patients with Idiopathic Intracranial Hypertension (IIH) and mild visual loss. **Methods**: Participants with IIH and mild visual loss who received a low-sodium weight-reduction diet were randomly assigned acetazolamide or matching placebo. **Results**: The mean improvement in visual loss was greater with acetazolamide than with placebo. Mean improvements in papilledema grade and vision-related quality of life were also observed with acetazolamide. **Conclusions**: In patients with IIH and mild visual loss, the use of acetazolamide with a low-sodium weight-reduction diet compared with diet alone resulted in modest improvement in visual field function.

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OR Orthopedic Surgery

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Acronyms

ABI	ankle brachial index	DDH	developmental dysplasia of the hip	MCL	medial collateral ligament	RA	rheumatoid arthritis
AC	acromioclavicular	DRUJ	distal radioulnar joint	M	metatarsal	RCD	rotator cuff disease
ACL	anterior cruciate ligament	DVT	deep vein thrombosis	MTP	metatarsophalangeal	ROM	range of motion
AIN	anterior interosseous nerve	EtOH	ethanol/alcohol	MVC	motor vehicle collision	RSD	reflex sympathetic dystrophy
AP	anteroposterior	FAI	femoroacetabular impingement	NVS	neurovascular status	SCFE	slipped capital femoral epiphysis
ARDS	acute respiratory distress syndrome	FOOSH	fall on outstretched hand	NWB	non-weight bearing	SLAP	superior labrum, anterior posterior
AVN	avascular necrosis	GA	general anesthetic	OA	osteoarthritis	SN	sensitivity
CA	coracoacromial	HO	heterotopic ossification	ORIF	open reduction internal fixation	THA	total hip arthroplasty
CC	coracoclavicular	I&D	incision and drainage	PCL	posterior cruciate ligament	TSA	total shoulder arthroplasty
CRPS	complex regional pain syndrome	IM	intramedullary	PE	pulmonary embolism	WB	weight-bearing
C&S	culture and sensitivity	LCL	lateral collateral ligament	PIN	posterior interosseous nerve	#	fracture
				PLC	posterolateral corner		

Basic Anatomy Review

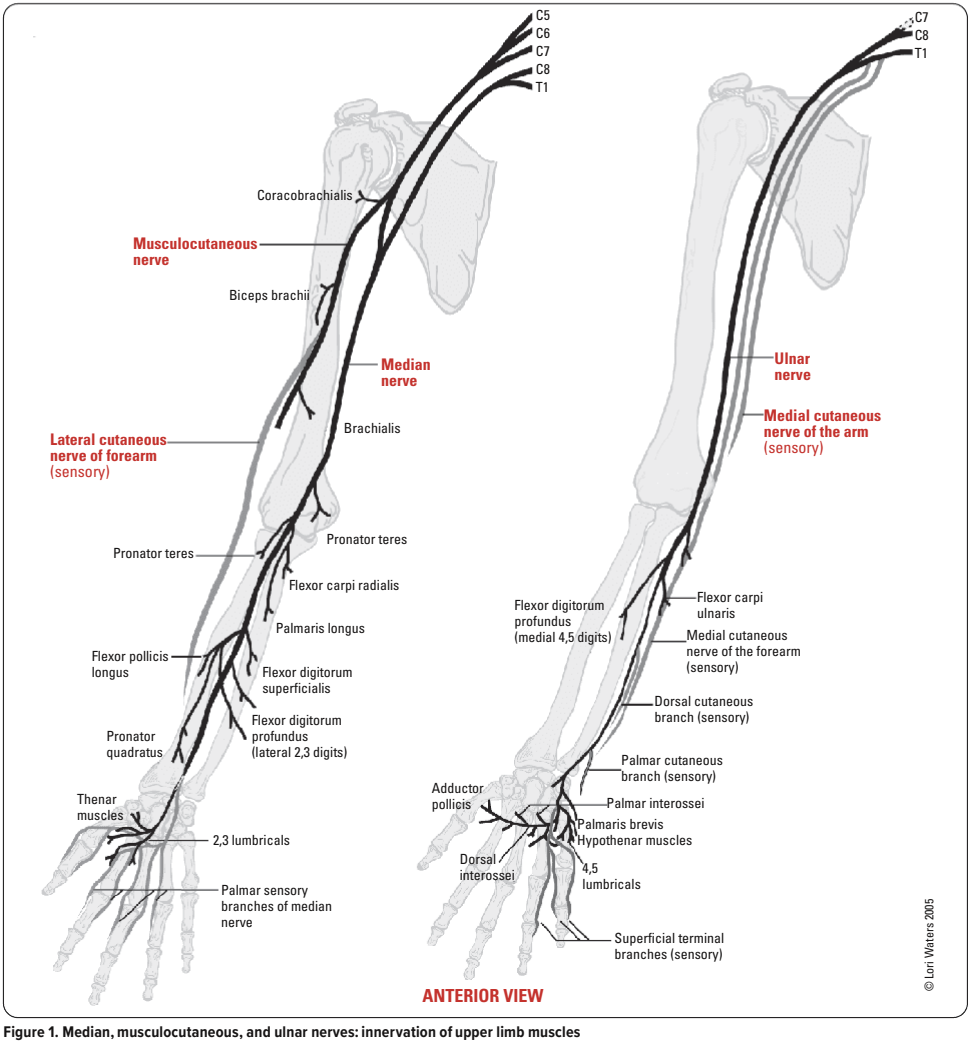


Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles

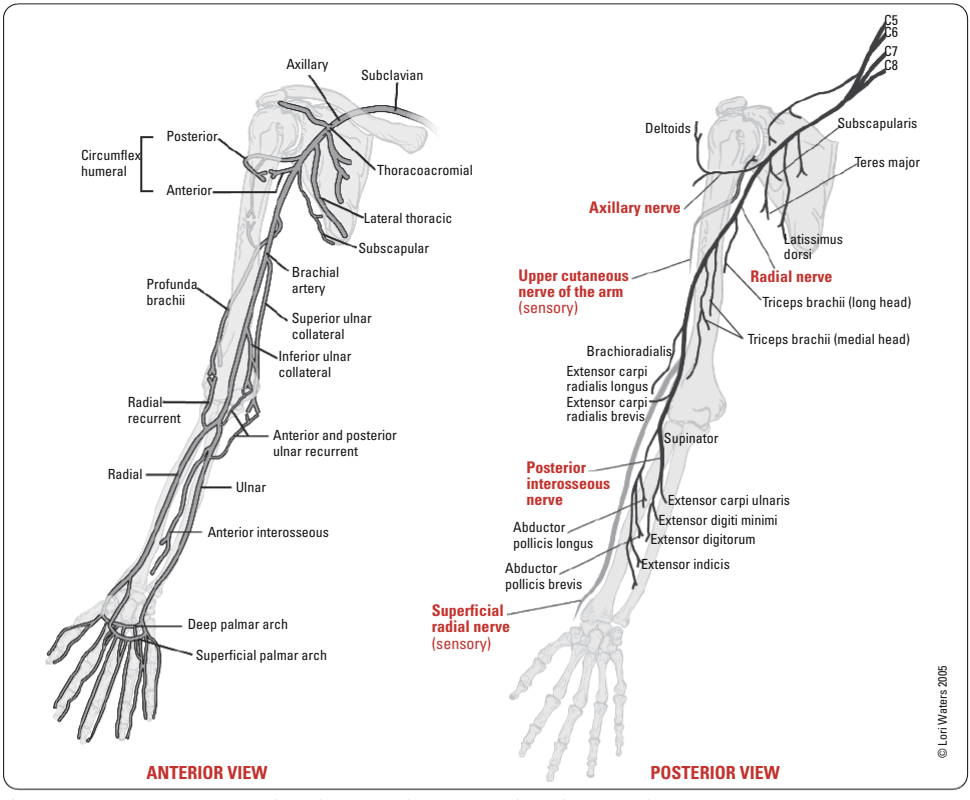


Figure 2. (Left) Blood supply to the upper limb, (Right) Innervation of the upper limb: axillary and radial nerves

Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities

Nerve	Motor	Sensory	Nerve Roots
Axillary	Deltoid/Teres Minor/Triceps (long head)	Lateral upper arm (Sergeant's Patch)	C5, C6
Musculocutaneous	Biceps/Brachialis	Lateral forearm	C5, C6
Radial	Triceps (medial and lateral heads) Wrist/Thumb/Finger Extensors Wrist abductors	Lateral dorsum of the hand Medial upper forearm	C5, C6, C7, C8
Median	Wrist flexors Flexion of 1st-3rd digits	Palmar thumb to radial half of 4th digit, and the dorsal tips of digits 1 to radial half of digit 4	C6, C7
Ulnar	Wrist flexors and adductors Flexion of 4th-5th digits	Medial palm and dorsum of hand 5th digit and medial half of 4th digit	C8, T1
Tibial	Ankle plantar flexion Knee flexion Great toe flexion	Sole of foot	L5, S1
Superficial Peroneal	Ankle eversion	Dorsum of foot	L5, S1
Deep Peroneal	Ankle dorsiflexion and inversion Great toe extension	1st web space	L5, S1
Sural		Lateral foot	S1, S2
Saphenous		Anteromedial ankle	L3, L4

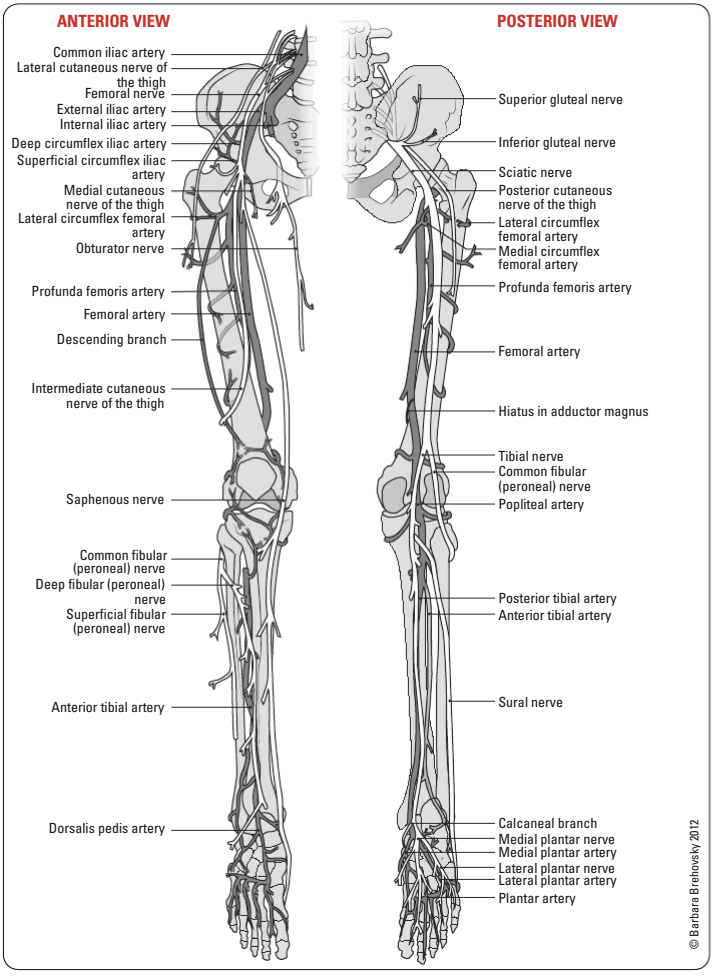


Figure 3. Nerves and arteries of lower limbs

Table 2. Muscle and Compartment Review of the Limbs

	Arm	Forearm	Thigh	Leg
Anterior Compartment	Biceps Brachii Brachialis Coracobrachialis	Pronator Teres Flexor Carpi Radialis Palmaris Longus Flexor Carpi Ulnaris Flexor Digitorum Superficialis Flexor Digitorum Profundus Flexor Pollicis Longus Pronator Quadratus	Sartorius Quadriceps Rectus Femoris Vastus Lateralis Vastus Intermedius Vastus Medialis	Tibialis Anterior Extensor Hallucis Longus Extensor Digitorum Longus Peroneus tertius
Posterior Compartment	Triceps Aconeus	Brachioradialis Extensor Carpi Radialis Longus Extensor Carpi Radialis Brevis Extensor Carpi Ulnaris Extensor Digitorum Extensor Digiti Minimi Abductor Pollicis Longus Extensor Pollicis Longus Extensor Pollicis Brevis Extensor Indicis Supinator	**Hamstrings** Semitendinosus Semimembranosus Biceps Femoris	**Superficial** Gastrocnemius Soleus Plantaris **Deep** Popliteus Flexor Hallucis Longus Flexor Digitorum Longus Tibialis Posterior
Medial Compartment			Adductor Longus Adductor Brevis Adductor Magnus Gracilis Pectineus	
Lateral Compartment				Peroneus Longus Fibularis Brevis

Fractures – General Principles

Fracture Description

1. Name of Injured Bone

2. Integrity of Skin/Soft Tissue

- closed: skin/soft tissue over and near fracture is intact
- open: skin/soft tissue over and near fracture is lacerated or abraded, such that fracture site can communicate with contaminants (i.e. outside environment or bowel)
- signs of an open fracture: continuous bleeding from puncture site or fat droplets in blood

3. Location

- epiphyseal: end of bone, forming part of the adjacent joint
- metaphyseal: the flared portion of the bone at the ends of the shaft
- diaphyseal: the shaft of a long bone (proximal, middle, distal)
- physis: growth plate

4. Orientation/Fracture Pattern (see *Figure 4, OR6*)

- transverse: fracture line perpendicular (<30° of angulation) to long axis of bone; result of direct high energy force
- oblique: angular fracture line (30°-60° of angulation); result of angulation and compressive force, high energy
- butterfly: triangular or wedge-shaped fragment resembling a butterfly; commonly between the two main fracture fragments in comminuted long bone fractures
- segmental: a separate segment of bone bordered by fracture lines; often the result of high-energy force
- spiral: complex, multi-planar fracture line; result of rotational force, low energy
- comminuted/multi-fragmentary: >2 fracture fragments
- intra-articular: fracture line crosses articular cartilage and enters joint
- compression: impaction of bone; typical sites are vertebrae or proximal tibia
- torus: compression of bony cortex on one side while the other remains intact, often seen in children (see *Figure 51, OR45*)
- greenstick: compression of one side with fracture of the opposite cortex, often seen in children (see *Figure 51, OR45*)
- pathologic: fracture through abnormal bone weakened by disease (e.g. tumour)

Displacement
Refers to position of the distal fragment relative to the proximal fragment

Varus/Valgus Angulation
Refers to the distal segment of the bone compared to the proximal segment
Varus = Apex away from midline
Valgus = Apex toward midline

Quick Upper Extremity Motor Nerve Exam
"Thumbs Up": PIN (Radial Nerve)
"OK Sign": AIN (Median Nerve)
"Spread Fingers": Ulnar Nerve

X-Ray Rule of 2s
2 sides = bilateral
2 views = AP + lateral
2 joints = joint above + below
2 times = before + after reduction

Sample Fracture Description
Closed (overlying skin integrity) spiral fracture (fracture pattern) of the distal third (location) of the left tibia (injured bone), with mild varus angulation lateral translation (alignment of fracture fragments). The fracture does not extend to the joint surface

5. Alignment of Fracture Fragments (see Figure 5)

- non-displaced: fracture fragments are in anatomic alignment
- displaced: fracture fragments are not in anatomic alignment
- distracted: fracture fragments are separated by a gap (opposite of compression)
- translated: percentage of overlapping bone at fracture site
- angulated: direction of fracture apex (e.g. varus/valgus)
- rotated: fracture fragment rotated about long axis of bone
- shortened: fracture fragments are compressed, resulting in shortened bone
- avulsion: tendon or ligament tears/pulls off bone fragment

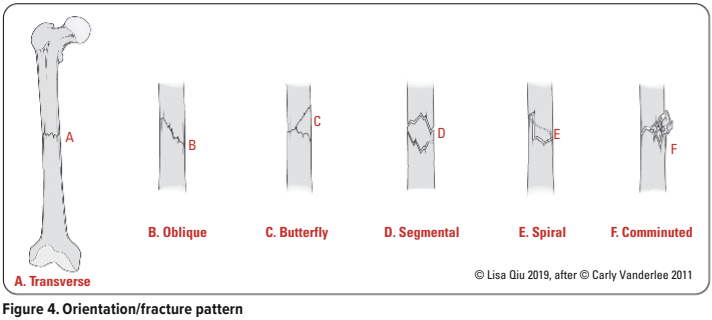


Figure 4. Orientation/fracture pattern

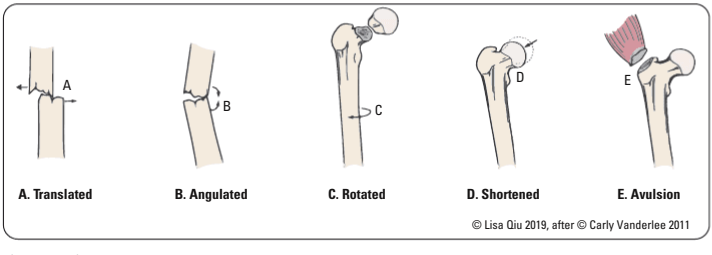


Figure 5. Alignment of fracture fragments

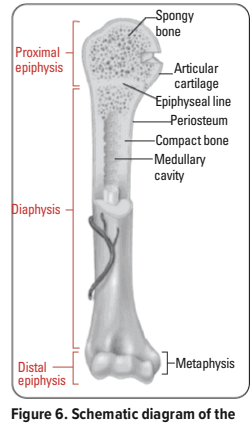


Figure 6. Schematic diagram of the long bone

Approach to Fractures

1. Clinical Assessment
   - ABCs, primary survey, and secondary survey (Advanced Trauma Life Support (ATLS) protocol)
     - assess for life threatening injury
     - assess for open and other fractures
   - AMPLE- F history (minimum): Allergies, Medications, Past medical history, Last meal, Events (mechanism of injury), Function pre-injury
     - previous significant injury or surgery to affected area
     - consider pathologic fracture with history of only minor trauma
   - physical exam: inspect (deformity, soft tissue integrity); palpate (maximal tenderness, NVS- document best possible neurovascular exam, avoid ROM/moving injured area to prevent exacerbation)

2. Analgesia
   - oral, IV, or local (e.g. hematoma block)

3. Imaging (see *Orthopedic X-Ray Imaging, OR8*)

4. Reduction: closed vs. open
   - closed reduction (with IV sedation and muscle relaxation if necessary)
     - apply traction in the long axis of the limb
     - reverse the mechanism that produced the fracture
   - open reduction
     - "NO CAST" (see sidebar)
     - other indications include
       - failed closed reduction
       - unable to cast or apply traction due to site
       - pathologic fractures
       - potential for improved function and/or outcomes with ORIF
   - ALWAYS re-check and document NVS after reduction and obtain post-reduction x-ray

Reasons for Closed Reduction and Splinting

Pain control

Reduces further damage to vessels, nerves, and skin and may improve neurovascular status

Reduces point loading on articular surfaces

Decreases risk of inadvertently converting closed to open fracture

Facilitates patient transport

Indications for Open Reduction

NO CAST
Non-union
Open fracture
Neurovascular **C**ompromise
Displaced intra-**A**rticular fracture
Salter-Harris 3,4,5
Poly**T**rauma

5. Immobilization
- external stabilization: splints, casts, traction, external fixator
- internal stabilization: percutaneous pinning, extramedullary fixation (screws, plates, wires), IM fixation (rods)

6. Follow-up
- evaluate stages of bone healing (see *Fracture Healing*)

7. Rehabilitation
- recommend rehabilitation when appropriate to regain function and avoid joint stiffness

Buck's Skin Traction
A system of weights, pulleys, and ropes that are attached to the end of a patient's bed exerting a longitudinal force on the distal end of a fracture, improving its length, alignment, and rotation temporarily while awaiting fixation (typically used for lower extremity fractures)

Fracture Healing

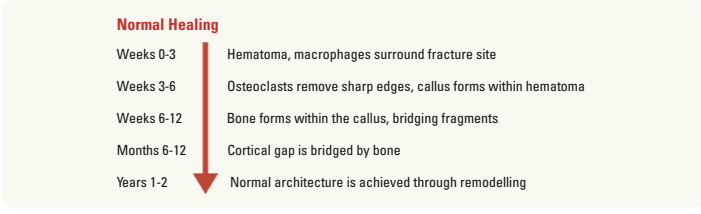

Normal Healing
Weeks 0-3
Hematoma, macrophages surround fracture site
Weeks 3-6
Osteoclasts remove sharp edges, callus forms within hematoma
Weeks 6-12
Bone forms within the callus, bridging fragments
Months 6-12
Cortical gap is bridged by bone
Years 1-2
Normal architecture is achieved through remodelling

Figure 7. Stages of bone healing

Wolff's Law
Bone adapts to the amount of force applied by increasing or decreasing its mass to resist the applied stress

Evaluation of Healing: Tests of Union
- clinical: no longer tender to palpation, no mobility, minimal or no deformity on physical exam
- x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

General Fracture Complications

Table 3. General Fracture Complications

	Early	Late
Local	Compartment syndrome Neurological injury Vascular injury Infection Implant failure Fracture blisters	Mal-/non-union AVN Osteomyelitis Heterotopic ossification Post-traumatic OA Joint stiffness/adhesive capsulitis CRPS type I/RSD
Systemic	Sepsis DVT PE ARDS secondary to fat embolism Hemorrhagic shock	

Fracture Blister
Formation of vesicles or bullae that occur on edematous skin overlying a fractured bone

Heterotopic Ossification
The formation of bone in abnormal locations (e.g. in muscle), secondary to pathology

CRPS/RSD
Sustained sympathetic activity characterized by pain out of proportion to physical exam findings, symptoms of hyperalgesia and allodynia, and signs of autonomic dysfunction (temperature asymmetry, mottling, hair or nail changes)

Articular Cartilage

Properties
- hyaline cartilage
- 2-4 mm layer covering ends of articulating bones, provides nearly frictionless surface
- avascular (nutrition from synovial fluid), aneural, alymphatic

ARTICULAR CARTILAGE DEFECTS

Etiology
- overt trauma, repetitive minor trauma (such as repetitive ankle sprains or patellar maltracking)
- degenerative conditions such as early stage OA or osteochondritis dissecans

Clinical Features
- part of OA presentation: pain with movement, decreased range of motion, joint line pain with possible effusion
- have predisposing factors such as: ligament injury; malalignment of the joint (e.g. varus or valgus); obesity; AVN; and inflammatory arthropathy
- may have mechanical symptoms of locking or catching related to the torn/displaced cartilage

Investigations
- x-ray (to rule out bony defects and check alignment)
- MRI (if x-ray is normal; MRI is not needed to assess cartilage loss associated with OA)

Avascular Necrosis
Ischemia of bone due to disrupted blood supply; most commonly affecting the femoral head, talus, or proximal scaphoid

Osteochondritis Dissecans
Avascular necrosis of subchondral bone most often occurring in children and adolescents causing pain and potentially hindering joint motion

Table 4. Outerbridge Classification of Chondral Defects

Grade	Chondral Damage
I	Softening and swelling of cartilage
II	Fragmentation and fissuring <1/2" in diameter
III	Fragmentation and fissuring >1/2" in diameter
IV	Erosion of cartilage down to bone

Treatment

- individualized
  - patient factors (age, skeletal maturity, activity level, etc.)
  - defect factors (Outerbridge Classification, subchondral bone involvement, etc.)
- non-operative
  - rest, COX2 inhibitors, NSAIDs, bracing, physiotherapy, intra-articular corticosteroids
- operative
  - microfracture, osteochondral grafting (autograft or allograft), autologous chondrocyte implantation

Orthopedic X-Ray Imaging

General Principles - "Rule of 2s"

- x-ray the joint above and below
- obtain at least 2 orthogonal views ± specialized views
- 2 sides, as needed for comparison

Sample radiograph description: "There is a simple transverse fracture of the proximal right humerus diaphysis. There is 1 cm of shortening. The distal fragment is medially angulated 70 degrees"

When reading a radiograph consider

- open or closed fracture (air/gas seen in the soft tissue)
- the view
- anatomical location
- laterality (right vs. left)
- skeletally mature vs. immature
- intra-articular vs. extra-articular
- joint congruent, subluxed, or dislocated
- rotation
- angulation
- displacement
- shortening

Table 5. Orthopedic X-Ray Imaging

Site	Injury	X-Ray Views
Shoulder	Anterior dislocation Posterior dislocation AC separation	AP Axillary ± stress view with 10 lb in hand Trans-scapular Zanca view (10-15 cephalic tilt)
Arm	Humerus #	AP Lateral
Elbow/Forearm	Supracondylar # Radial head # Monteggia # Nightstick # Galeazzi #	AP Lateral
Wrist	Colles' # Smith # Scaphoid #	AP Lateral Clenched Fist (for scapholunate dissociation)
Pelvis	Pelvic #	AP pelvis Inlet and outlet views Judet views (obturator and iliac oblique for acetabular #)
Hip	Femoral head/neck # Intertrochanteric # Arthritis SCFE FAI Developmental dysplasia of the hip (DDH)	AP Lateral Frog-leg lateral Dunn False profile
Knee	Knee dislocation Femur/tibia # Patella # Patella dislocation Patella femoral syndrome	AP standing, lateral Skyline (tangential view with knees flexed at 45° to see patellofemoral joint)
Leg	Tibia shaft # Fibula shaft #	AP Lateral

Table 5. Orthopedic X-Ray Imaging

Site	Injury	X-Ray Views
Ankle	Ankle #	AP Lateral Mortise view (ankle at 15° of internal rotation)
Foot	Talar # Calcaneal # MT # Lisfranc injuries	AP Lateral Oblique Lateral, Harris, axial
Spine	Compression # Burst # Cervical spine #	AP spine AP odontoid Lateral Oblique Swimmer's view (lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate) Lateral flexion/extension view: evaluate subluxation of cervical vertebrae

Orthopedic Emergencies

Trauma Patient Workup

Etiology
- high energy trauma (e.g. MVC, fall from height)
- may be associated with spinal injuries or life-threatening visceral injuries

Clinical Features
- comminuted, open fractures with significant soft tissue injury
- local swelling, tenderness, deformity of the limbs, and instability of the pelvis or spine
- decreased level of consciousness, hypotension, hypovolemia
- consider involvement of EtOH or other psychoactive substances

Investigations
- trauma survey (see Emergency Medicine, ER2)
- x-rays: lateral cervical spine, AP chest, AP pelvis, AP and lateral of all bones suspected to be injured
- CT is also utilized to inspect for musculoskeletal injuries in the trauma setting
- other views of pelvis: AP, inlet, and outlet; Judet views for acetabular fracture (see *Table 19, OR30*)

Treatment
- ABCDEs: initiate resuscitation for life-threatening injuries (ATLS protocol)
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- if patient unstable then Damage Control Orthopedics – use of external fixation for fractures initially and then bring patient back to OR for definitive fixation (IM nail or ORIF) once hemodynamically stable
- DVT prophylaxis once stable

Complications
- hemorrhage – life-threatening (may produce signs and symptoms of hypovolemic shock)
- fat embolism syndrome – SOB, hypoxemia, petechial rash, thrombocytopenia, and neurological symptoms
- venous thromboembolism – DVT and PE
- bladder/urethral/bowel injury
- neurological and vascular damage
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic OA of joints with intra-articular fractures
- sepsis and/or tetanus infection especially if missed open fracture

Orthopedic Emergencies

VON CHOP
Vascular compromise
Open fracture
Neurological compromise/cauda equina syndrome
Compartment syndrome
Hip dislocation
Osteomyelitis/septic arthritis
Unstable **P**elvic fracture

Controversies in Initial Management of Open Fractures
Scand J Surg 2014;103(2):132-137
Literature review examining the initial management of open fractures. 40 studies included.
Findings:
A first-generation cephalosporin (or clindamycin) should be administered upon arrival. In general, 24 h of antibiotics after each debridement is sufficient to reduce infection rates.
Although cultures are taken from delayed (>24 h) or infected injuries, it may not be necessary to routinely take post-debridement cultures in open fractures.
Open fractures should be debrided as soon as possible, although the "6 h rule" is not generally valid.
Wounds should be closed within 7 d once soft tissue has stabilized and all non-viable tissue removed.
Negative pressure wound therapy (NPWT) has been shown to decrease infection rates in open fractures.

Open Fractures

• fractured bone and hematoma in communication with the external or contaminated environment

Emergency Measures

• ABCs, primary survey, and resuscitate as needed
• remove obvious foreign material once in a controlled hospital environment
• irrigate with normal saline if grossly contaminated
• cover wound with sterile dressings
• immediate IV antibiotics
• tetanus toxoid or immunoglobulin as needed (see Plastic Surgery, PL28)
• NPO and prepare for OR (blood work, consent, ECG, CXR)
  ▪ operative irrigation and debridement within 6-8 h to decrease risk of infection
  ▪ ORIF
  ▪ traumatic wound may be left open to drain with vacuum-assisted closure if necessary
  ▪ re-examine with repeat irrigation and debridement in 48 h if necessary

Table 6. Gustilo Classification of Open Fractures

Gustilo Grade	Length of Open Wound	Description	Prophylactic Antibiotic Regimen
I	<1 cm	Minimal contamination and soft tissue injury Simple or minimally comminuted fracture	First generation cephalosporin (cefazolin) 2 g IV q8 h for 2 d If allergy use clindamycin 900 mg IV q8 h If MRSA positive use vancomycin 15 mg/kg IV q12 h
II	1-10 cm	Moderate contamination Moderate soft tissue injury	As per Grade I
III*	>10 cm	IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound IIIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound IIIC: Vascular injury/compromise	First generation cephalosporin (cefazolin) for 2 d plus Gram-negative coverage (gentamicin or ceftriaxone) for at least 3 d For soil or fecal contamination, metronidazole is added for anaerobic coverage ± penicillin G If MRSA positive use vancomycin 15 mg/kg IV q12 h

*Any high energy, comminuted fracture, shot gun, farmyard/soil/water contamination, exposure to oral flora, or fracture >8 h old is immediately classified as Grade III

33% of patients with open fractures have multiple injuries

Antibiotic Prophylaxis in the Management of Open Fractures
JBJS Reviews: 2019 Feb;7(2):e1
Purpose: Provide current practice recommendations on prophylaxis for patients with open fractures of the extremities.
Methods: Systematic survey of publications from January 2007 to June 2017, and search of WorldCat for textbooks and websites for institutional guidelines.
Results: Most recommendations suggested Gram-positive antibiotics up to 3 d post-injury for less severe injuries. For more severe injuries, most recommendations included broad spectrum antibiotics for 2-3 d. As well, most sources recommend immediate IV administration of antibiotics.
Support early systemic prophylaxis for patients with open fractures of the extremities. However, differences are seen across antibiotic regimens, doses, and duration of administration.

Cauda Equina Syndrome

• see Neurosurgery, NS32

Compartment Syndrome

• increased interstitial pressure in an anatomical compartment (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment), with little room for expansion
• interstitial pressure exceeds capillary perfusion pressure, leading to irreversible muscle necrosis (in 4-6 h) and eventually nerve necrosis

Etiology

• intracompartmental
  ▪ fracture (particularly tibial shaft or pediatric supracondylar and forearm fractures)
  ▪ reperfusion injury, crush injury, or ischemia
• extracompartmental: constrictive dressing (circumferential cast), poor position during surgery, circumferential burn

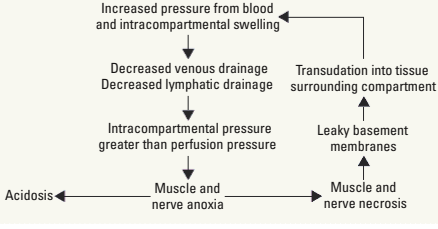

Increased pressure from blood and intracompartmental swelling
Decreased venous drainage
Decreased lymphatic drainage
Transudation into tissue surrounding compartment
Intracompartmental pressure greater than perfusion pressure
Leaky basement membranes
Acidosis
Muscle and nerve anoxia
Muscle and nerve necrosis

Figure 8. Pathogenesis of compartment syndrome

Most important sign is increased pain with passive stretch. Most important symptom is pain out of proportion to injury

5 Ps of Compartment Syndrome
Pain: out of proportion for injury and not relieved by analgesics
  Increased pain with passive stretch of compartment muscles
Pallor: late finding
Paresthesia
Paralysis: late finding
Pulselessness: late finding

Clinical Features
- pain out of proportion to injury (typically first and most significant symptom)
- pain with active contraction of compartment
- pain with passive stretch (most sensitive sign)
- swollen, tense compartment
- suspicious history

- **5 Ps**: late sign – do not wait for these to develop to make the diagnosis!

Investigations
- compartment syndrome is a clinical diagnosis; investigations usually not necessary
- in children, unconscious patients, or associated peripheral nerve injury where clinical exam is unreliable, compartment pressure monitoring with catheter (normal = 0 mmHg; elevated ≥30 mmHg or (dBP – measured pressure) ≤30 mmHg)

Treatment
- non-operative
  - remove constrictive dressings (casts, splints), elevate limb to the level of the heart
- operative
  - urgent fasciotomy
  - 48-72 h postoperative: necrotic tissue debridement + wound closure
  - may require delayed closure and/or skin grafting

Complications
- Volkmann's ischemic contracture: ischemic necrosis of muscle; followed by secondary fibrosis; and finally calcification - especially following supracondylar fracture of humerus
- rhabdomyolysis, renal failure secondary to myoglobinuria

Osteomyelitis

- bone infection with progressive inflammatory destruction

Etiology
- most commonly caused by S. aureus
- mechanism of spread: hematogenous (most common) vs. direct-inoculation vs. contiguous focus
- risk factors: recent trauma/surgery, immunocompromised patients, DM, IV drug use, poor vascular supply, peripheral neuropathy

Clinical Features
- symptoms: pain and fever
- on exam: erythema, tenderness, edema common ± abscess/draining sinus tract; impaired function/WB

Diagnosis
- see Medical Imaging, MI24 and MI27
- workup may include: WBC and differential, ESR, CRP, blood culture, aspirate culture/bone biopsy

Table 7. Treatment of Osteomyelitis

Acute Osteomyelitis	Chronic Osteomyelitis
IV antibiotics 4-6 wk; started empirically and adjusted after obtaining blood and aspirate cultures	Surgical debridement
± surgery (I&D) for abscess or significant involvement	Antibiotics: both local (e.g. antibiotic beads) and systemic (IV)
± hardware removal (if present)	

Septic Arthritis

- joint infection with progressive destruction if left untreated

Etiology
- most commonly caused by *S. aureus* in adults
- consider coagulase-negative *Staphylococcus* in patients with prior joint replacement
- consider *N. gonorrhoeae* in sexually active adults, and newborns
- most common route of infection is hematogenous
- risk factors: young/elderly (age >80 yr), prosthetic joint, recent joint surgery, skin infection/ulcer, IV drug use, recent intra-articular corticosteroid injection, immunocompromised (cancer, DM, alcoholism, RA)

Plain Film Findings of Osteomyelitis

Soft tissue swelling

Lytic bone destruction*

Periosteal reaction (formation of new bone, especially in response to #)*

*Generally not seen on plain films until 10-12 d after onset of infection

Rapid progression of signs and symptoms (over hours) necessitates need for serial examinations

Acute osteomyelitis is a medical emergency which requires an early diagnosis and appropriate antimicrobial and surgical treatment

Joints most commonly affected by septic arthritis in descending order: knee ➔ hip ➔ elbow ➔ ankle ➔ sternoclavicular joint

Plain Film Findings in a Septic Joint

Early (0-3 d): usually normal; may show soft-tissue swelling or joint space widening from localized edema

Late (4-6 d): joint space narrowing and destruction of cartilage

Serial C-reactive protein (CRP) can be used to monitor response to therapy

Does This Adult Patient Have Septic Arthritis?
JAMA 2007;297(13):1478-1488
Purpose: To review the accuracy and precision of the clinical evaluation for the diagnosis of nongonococcal bacterial arthritis.
Methods: Review of 14 studies including 6242 patients of which 653 had positive synovial culture (gold standard diagnostic tool for septic arthritis).
Results: Age, diabetes mellitus, rheumatoid arthritis, joint surgery, hip or knee prosthesis, skin infection, and human immunodeficiency virus type 1 infection significantly increase the probability of septic arthritis. Joint pain, history of joint swelling, and fever are found in >50% of cases. The presence of increased WBC increases the likelihood ratio (for counts <25000/μL: LR, 0.32; 95% CI, 0.23-0.43; for counts ≥25000/μL: LR, 2.9; 95% CI, 2.5-3.4; for counts ≥100000/μL: LR, 28.0; 95% CI, 12.0-66.0). A polymorphonuclear cell count of ≥90% increases the LR of septic arthritis by 3.4, while a PMN cell count of <90% reduces the LR by 0.34.
Conclusions: Clinical findings may be used to identify patients with monoarticular arthritis who may have septic arthritis. Laboratory findings from an arthrocentesis are also required and helpful prior to Gram stain and culture.

Clinical Features
- inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling, pain on active and passive ROM, ± fever

Investigations
- x-ray (to rule out fracture, tumour, metabolic bone disease), ESR, CRP, WBC, blood cultures
- joint aspirate: cloudy yellow fluid, WBC >50000 with >90% neutrophils, protein level >4.4 mg/dL, joint glucose level <60% blood glucose level, no crystals, positive Gram stain results
- listen for heart murmur (if concern for infective endocarditis, use Duke Criteria)

Treatment
- IV antibiotics, empiric therapy (based on age and risk factors), adjust following joint aspirate C&S results
- non-operative
  - therapeutic joint aspiration, serially if necessary
- operative
  - arthroscopic or open irrigation and drainage

Shoulder

Shoulder Dislocation

- complete loss of continuity between the two articular surfaces of the glenohumeral joint; may be anterior or posterior

Investigations
- anterior dislocation x-rays: AP, trans-scapular, and axillary views of the shoulder
- posterior dislocation x-rays: AP, trans-scapular, and axillary views of the shoulder; or CT scan

Table 8. Anterior and Posterior Shoulder Dislocation

	Anterior Shoulder Dislocation (>90%)	Posterior Shoulder Dislocation (5%)
MECHANISM		
	Abducted externally rotated/hyperextended arm Blow to posterior shoulder Involuntary, usually traumatic; voluntary, atraumatic	Adducted, internally rotated, flexed arm FOOSH 3 Es (epileptic seizure, EtOH, electrocution) Blow to anterior shoulder
CLINICAL FEATURES		
Symptoms	Pain, arm slightly abducted and externally rotated with inability to internally rotate	Pain, arm is held in adduction and internal rotation; external rotation is blocked
Shoulder Exam	**"Squared off" shoulder** **Positive apprehension test**: patient looks apprehensive with gentle shoulder abduction and external rotation to 90° as humeral head is pushed anteriorly and recreates feeling of anterior dislocation **Positive relocation test**: a posteriorly directed force applied during the apprehension test relieves apprehension since anterior subluxation is prevented **Positive sulcus sign**: presence of subacromial indentation with distal traction on humerus indicates inferior shoulder instability These tests are more commonly used for chronic recurrent instability	**Anterior shoulder flattening**, prominent coracoid, palpable mass posterior to shoulder **Positive posterior apprehension ("jerk") test**: with patient supine, flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will "jerk" back with the sensation of subluxation Note: the posterior apprehension test is used to test for recurrent posterior instability, NOT for acute injury
Neurovascular Exam Including	**Axillary nerve**: sensory patch over deltoid and deltoid contraction **Musculocutaneous nerve**: sensory patch on lateral forearm and biceps contraction	Full neurovascular exam as per anterior shoulder dislocation
RADIOGRAPHIC FINDINGS		
Axillary View	Humeral head is anterior	Humeral head is posterior
Trans-scapular 'Y' View	Humeral head is anterior to the centre of the "Mercedes-Benz"sign	Humeral head is posterior to center of "Mercedes-Benz" sign
AP View	Sub-coracoid lie of the humeral head is most common	Partial vacancy of glenoid fossa (vacant glenoid sign) and >6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign)
Hill-Sachs and Bony Bankart Lesions	**± Hill-Sachs lesion**: compression fracture of posterior humeral head due to forceful impaction of an anteriorly dislocated humeral head against the glenoid rim **± Bony Bankart lesion**: avulsion of the anterior glenoid labrum (with attached bone fragments) from the glenoid rim	**± Reverse Hill-Sachs lesion** (75% of cases): divot in anterior humeral head **± Reverse bony Bankart lesion**: avulsion of the posterior glenoid labrum from the bony glenoid rim

Posterior Shoulder Dislocation
Up to 60-80% are missed on initial presentation due to poor physical exam and radiographs

There are 4 Joints in the Shoulder
Glenohumeral, AC, sternoclavicular (SC), scapulothoracic

Shoulder passive ROM: abduction – 180°, adduction – 45°, flexion – 180°, extension – 45°, int. rotation – level of T4, ext. rotation – ~90° likely more...

Factors Causing Shoulder Instability
- Shallow glenoid
- Loose capsule
- Ligamentous laxity

Frequency of Dislocations
- Anterior shoulder > Posterior shoulder
- Posterior hip > Anterior hip
- The glenohumeral joint is the most commonly dislocated joint in the body since stability is sacrificed for motion

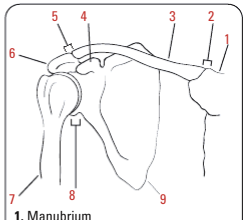


Figure 9. Shoulder joints

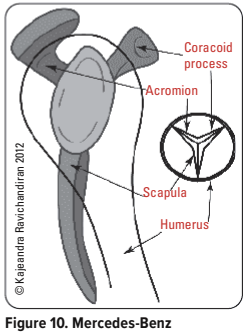


Figure 10. Mercedes-Benz

Table 8. Anterior and Posterior Shoulder Dislocation

	Anterior Shoulder Dislocation (>90%)	Posterior Shoulder Dislocation (5%)
TREATMENT		
	Closed reduction with IV sedation and muscle relaxation **Traction-countertraction**: assistant stabilizes torso with a folded sheet wrapped across the chest while the surgeon applies gentle steady traction **Stimson**: while patient lies prone with arm hanging over table edge, hang a 5 lb weight on wrist for 15-20 min Hippocratic method: place heel into patient's axilla and apply traction to arm Cunningham's method: gentle longitudinal support and traction of the arm at the patient's side, massage/relaxation of deltoid, trapezius, and biceps to allow atraumatic shoulder reduction. Low-risk, low pain; if not successful try above methods Obtain post-reduction x-rays Check post-reduction NVS Sling x 3 wk (avoid abduction and external rotation), followed by shoulder rehabilitation (dynamic stabilizer strengthening)	Closed reduction with IV sedation and muscle relaxation Inferior traction on a flexed elbow with pressure on the back of the humeral head Obtain post-reduction x-rays Check post-reduction NVS Sling in abduction and external rotation x 3 wk, followed by shoulder rehabilitation (dynamic stabilizer strengthening)

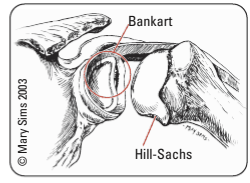


Figure 11. Posterior view of anterior dislocation causing Hill-Sachs and Bankart lesions

Prognosis

- recurrence rate depends on age of first dislocation
- <20 yr = 65-95%; 20-40 yr = 60-70%; >40 yr = 2-4%

Specific Complications

- recurrent dislocation (most common complication)
- unreduced dislocation
- shoulder stiffness
- rotator cuff, capsular, or labral tear (Bankart/SLAP lesion)
- injury to axillary nerve/artery, brachial plexus

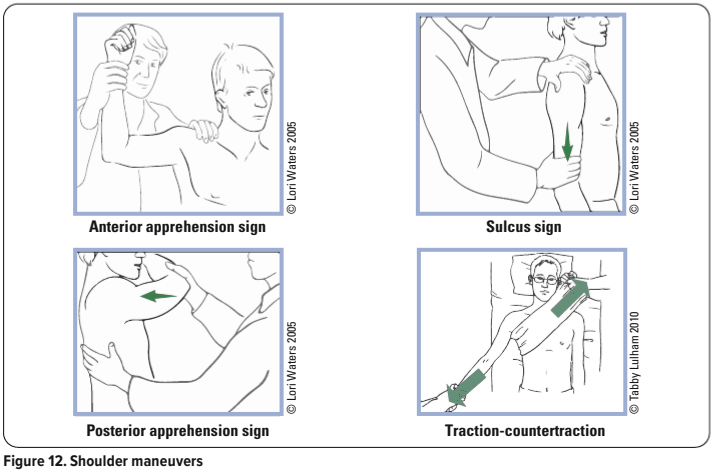


Figure 12. Shoulder maneuvers

Rotator Cuff Disease

- rotator cuff consists of 4 muscles that act to stabilize the humeral head within the glenoid fossa

Table 9. Rotator Cuff Muscles (SITS)

Muscle	Muscle Attachments		Nerve Supply	Muscle Function
	Proximal	Distal		
Supraspinatus	Scapula	Greater tuberosity of humerus	Suprascapular nerve	Abduction
Infraspinatus	Scapula	Greater tuberosity of humerus	Suprascapular nerve	External rotation
Teres Minor	Scapula	Greater tuberosity of humerus	Axillary nerve	External rotation
Subscapularis	Scapula	Lesser tuberosity of humerus	Subscapular nerve	Internal rotation and adduction

SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

Etiology

- narrowing of subacromial space
- most commonly due to a relative imbalance of rotator cuff and larger shoulder muscles, allowing for superior translation and subsequent wear of the rotator cuff muscle tendons
  - glenohumeral (rotator cuff) muscle weakness leading to abnormal motion of humeral head
  - scapular muscle weakness leading to abnormal motion of acromion – poor posture
- acromial abnormalities, such as congenital narrow space or osteophyte formation or Type III acromion morphology
  1. outlet/subacromial impingement: "painful arc syndrome," compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the undersurface of acromion, AC joint, and CA ligament
  2. bursitis and tendonitis
  3. rotator cuff thinning and tear if left untreated

Clinical Features

- insidious onset, but may present as an acute exacerbation of chronic disease, night pain, and difficulty sleeping on affected side
- pain worsens with active motion (especially overhead); passive movement generally permitted
- weakness and loss of ROM, especially between 90-130° (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity
- rule out bicep tendinosis (Speed's test) and SLAP lesions (O'Brien's test)

Investigations

- x-ray: AP view may show sclerosis of the undersurface of the acromion or greater tuberosity, high riding humerus relative to glenoid, indicating large tear, evidence of chronic tendonitis
- MRI: coronal/sagittal, oblique, and axial orientations are useful for assessing full/partial tears and tendinopathy ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
- arthrogram: not commonly used but can assess full thickness tears, difficult to assess partial tears
- ultrasound: may be a useful adjunct but limited ability to evaluate other intra-articular pathology

Treatment

- non-operative
  - first line treatment, rotator cuff injury treatment begins with physiotherapy (regardless of severity on MRI findings)
  - physiotherapy, activity modification, non-narcotic analgesia ± steroid injection
  - mild or moderate cases frequently improve
  - progression to surgery if necessary
- operative
  - severe tear or impingement that is refractory to 2-3 mo physiotherapy and 1-2 corticosteroid injections
  - arthroscopic or open surgical repair (i.e. acromioplasty, rotator cuff repair)

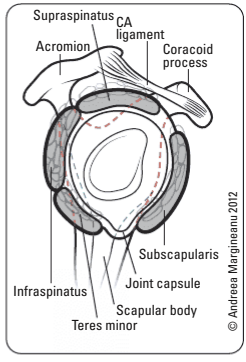


Figure 13. Lateral view of the muscles of the rotator cuff

Bigliani Classification of Acromion Morphology
- Type I – flat
- Type II – curved
- Type III – hooked

Screening Out Rotator Cuff Tears
- No night pain (SN 87.7%)
- No painful arc (SN 97.5%)
- No impingement signs (SN 97.2%)
- No weakness

Returning to the bedside: Using the history and physical examination to identify rotator cuff tears
J Am Geriatr Soc 2000;48:1633-1637

Ruling in Rotator Cuff Tears – 98% probability of rotator cuff tear if all 3 of the following are present:
Supraspinatus weakness
External rotation weakness
Positive impingement sign(s)
Diagnosis of rotator cuff tears.
Lancet 2001;357:769-770

Does this Patient with Shoulder Pain have Rotator Cuff Disease? The Rational Clinical Examination Systematic Review
JAMA 2013;310:837-847
Purpose: To conduct a meta-analysis to identify the clinical exam findings that most accurately detect rotator cuff disease (RCD).
Methods: 5 studies of sufficient quality were included. Sample size ranged from 30-203 shoulders, and the prevalence of RCD ranged from 33-81%.
Results/Conclusions: Among pain provocation tests, a positive painful arc test had the greatest specificity (SP) of 81% and sensitivity (SN) of 71%. Among strength tests, a positive external rotation lag test and internal rotation lag test were the most accurate for full-thickness tears (SP 47%, SN 94%; SP 97%, SN 83% respectively). The internal rotation lag test was therefore also the most accurate for identifying patients without a full-thickness tear. A positive drop arm test is helpful to identify patients with RCD (SN 24%, SP 93%).

Table 10. Rotator Cuff Special Tests

Test	Examination	Positive Test
Jobe's Test (i.e. Empty Can Test)	Supraspinatus: place the shoulder in 90° of abduction and 30° of horizontal flexion (from the scapular plane) and internally rotate the arm so that the thumb is pointing toward the floor	Weakness with active resistance suggests a supraspinatus tear
Lift-off Test	Subscapularis: internally rotate arm so dorsal surface of hand rests on lower back; patient instructed to actively lift hand away from back against examiner resistance (use Belly Press Test if too painful)	Inability to actively lift hand away from back suggests a subscapularis tear
Posterior-Cuff Test	Infraspinatus and teres minor: arm positioned at patient's side in 90° of flexion; patient instructed to externally rotate arm against the resistance of the examiner	Weakness with active resistance suggests posterior cuff tear
Neer's Test	Rotator cuff impingement: passive shoulder flexion	Pain elicited between 130-170° suggests impingement
Hawkins-Kennedy Test	Rotator cuff impingement: shoulder flexion to 90° and passive internal rotation	Pain with internal rotation suggests impingement
Painful Arc Test	Rotator cuff tendinopathy: patient instructed to actively abduct the shoulder	Pain with abduction >90° suggests tendinopathy
Speed's Test	Apply resistance to the forearm when the arm is in forward flexion with the elbows fully extended	Pain in the bicipital groove
O'Brien's Test	SLAP lesion: forward flexion of the arm to 90° while keeping the arm extended. Arm is adducted 10-15° Internally rotate the arm so thumb is facing down and apply a downward force. Repeat the test with arm externally rotated	Pain or clicking in the glenohumeral joint in internal rotation but not external rotation

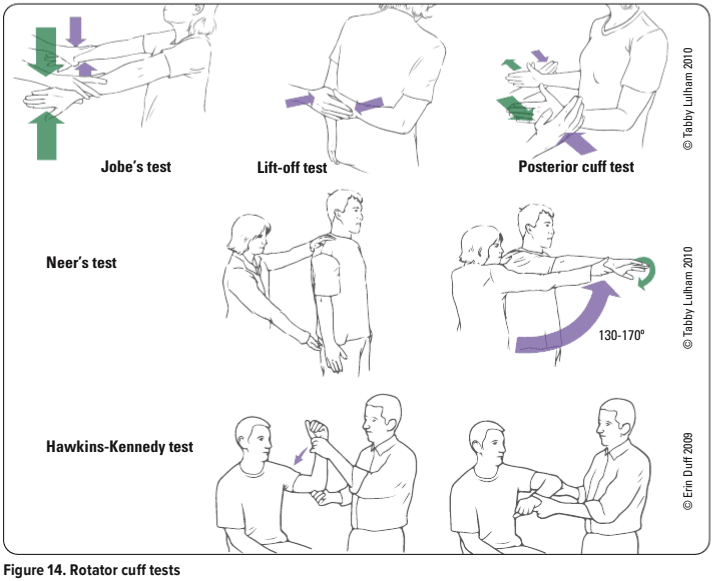


Figure 14. Rotator cuff tests

Acromioclavicular Joint Pathology

- subluxation or dislocation of AC joint
- 2 main ligament groups attach clavicle to scapula: AC and CC ligaments

Mechanism
- fall onto shoulder with adducted arm or direct trauma to point of shoulder (usually fall onto the posterosuperior aspect of the lateral shoulder)

Clinical Features
- pain with adduction of shoulder and/or palpation over AC joint
- palpable step deformity between distal clavicle and acromion (with dislocation) i.e. piano key sign
- limited ROM

Investigations
- x-rays: bilateral AP, Zanca view (10-15° cephalic tilt), axillary

Treatment
- non-operative
  - sling 1-3 wk, ice, analgesia, early ROM, and rehabilitation
- operative
  - indication: Rockwood Class IV-VI (III if labourer or high level athlete)
  - number of different approaches involving AC/CC ligament reconstruction or screw/hook plate insertion

Table 11. Rockwood Classification of Acromioclavicular Joint Separation

Grade	Features	Treatment
I	Joint sprain, absence of complete tear of either ligament	Non-operative
II	Complete tear of AC ligament, incomplete tear of CC ligament, without marked elevation of lateral clavicular head	Non-operative
III	Complete tear of AC and CC ligaments, >5 mm elevation at AC joint, superior aspect of acromion is below the inferior aspect of the clavicle	Most non-operative, operative if labourer or high level athlete Will heal with step deformity, although most fully functional in 4-6 mo
IV-VI	Based on the anatomical structure the displaced clavicle is in proximity to (posterior, very superior, inferior)	Operative in most cases

Grade	AC Ligament	CC Ligament	Reducible	Treatment
I	Sprained	Normal	N/A	Non-operative
II	Torn	Sprained	Yes	Non-operative
III	Torn	Torn	Yes	Most non-operative, operative if labourer or high-level athlete Will heal with step deformity, although most fully functional in 4-6 mo
IV-VI	Torn	Torn	No	Operative in most cases

Rockwood separations IV-VI are determined based on direction of displacement:
IV: Distal clavicle displaced posteriorly into trapezius (seen on axillary XR)
V: Distal clavicle herniated through deltotrapezial fascia into subcutaneous tissue
VI: Distal clavicle displaced inferior to acromion or coracoid under conjoined tendon (rare)

Clavicle Fracture

- incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
- common in children (unites rapidly without complications)

Mechanism
- fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

Clinical Features
- pain and tenting of skin
- arm is clasped to chest to splint shoulder and prevent movement

Investigations
- evaluate NVS of entire upper limb
- x-ray: AP, 45° cephalic tilt (superior/inferior displacement), 45° caudal tilt (AP displacement)
- CT: useful for medial physeal fractures and sternoclavicular injury

Pneumothorax or pulmonary contusion are potential complications of severe clavicle fracture, and rarely severe AC joint dislocation

Multicentre Randomized Clinical Trial of Nonoperative Versus Operative Treatment of Acute Acromio-Clavicular Joint Dislocation
Orthop Trauma. 2015 Nov;29(11):479-87.
Purpose: To compare the effectiveness of operative versus non-operative treatment of acute acromio-clavicular (AC) joint dislocations using modern surgical fixation.
Methods: This is a multicenter randomized clinical trial. Eighty three patients with acute (<28 d from the time of injury) complete (grade III, IV, and V) dislocations of the AC joint were randomized to operative repair (n=40) with hook plate fixation or to non-operative treatment (n=43). The primary outcome was Disabilities of the Arm, Shoulder and Hand (DASH) score at 1 yr after injury. Radiographic evaluation was also performed at 6 wk, and at 3, 6, 12, and 24 mo.
Results: The DASH scores (a disability score, lower score is better) were significantly improved in the non-operative group at 6 wk (operative, 45; nonoperative, 31; p=0.014) and 3 mo (operative, 29; nonoperative, 16; p=0.005). There were no significant differences between the groups at 6 mo, 1 yr, or 2 yr after injury. Although radiographic measures were superior in the operative group, the re-operation rate was significantly reduced in the non-operative group (p<0.05).
Conclusions: Although hook plate fixation improved radiographic alignment, it was not clinically superior to non-operative treatment of acute complete dislocations of the AC joint. The non-operative group had better early scores, but both groups improved from a significant level of initial disability to a good or excellent result. Currently, there is no clear evidence that operative treatment with the hook plate improves short-term outcome for complete AC joint dislocations.

Open Reduction and Internal Fixation vs. Nonsurgical Treatment in Displaced Midshaft Clavicle Fractures: A Meta-Analysis
J Orthop Trauma 2018;32(7):e276-e283
Purpose: Compare outcomes from ORIF and non-operative treatments in displaced mid-shaft clavicular fractures.
Methods: Meta-analysis with 9 RCTs reporting nonunion, functional outcomes, and subsequent surgeries in patients older than 16 yr.
Results: 9 randomized clinical trials with 1027 total patients were included. ORIF was associated with significantly lower nonunion rate of 1.7% compared to 14.5% for the non-operative treatment groups (RR 0.15, 95% CI, 0.08-0.31). Functional outcomes, rated by either DASH or Constant scores, were significantly better in ORIF up to 6 mo. When excluding elective plate removal, the rate of subsequent surgeries was significantly lower in the ORIF cohort (4.7% vs. 14%, RR 0.36, 95% CI 0.24-0.56).
Conclusions: ORIF is associated with significant reductions in nonunions and earlier functional outcomes in displaced midshaft clavicular fractures.

Treatment
- medial and middle-third clavicle fractures
  - for nondisplaced fractures, simple sling for 1-2 wk prn
  - early ROM and strengthening once pain subsides
  - if fracture is shortened >2 cm, consider ORIF
- distal-third clavicle fractures
  - undisplaced (with ligaments intact): sling for 1-2 wk
  - displaced (CC ligament injury): ORIF

Specific Complications (see *General Fracture Complications, OR7*)
- cosmetic bump (most common complication)
- shoulder stiffness, weakness with repetitive activity
- pneumothorax, brachial plexus injuries, and subclavian vessel (all very rare)

Associated Injuries with Clavicle Fractures
- Up to 9% of clavicle fractures are associated with other fractures (most commonly rib fractures)
- Majority of brachial plexus injuries are associated with proximal third fractures

Frozen Shoulder (Adhesive Capsulitis)

- disorder characterized by progressive pain and stiffness of the shoulder, usually resolving spontaneously within 18 mo

Mechanism
- primary adhesive capsulitis
  - idiopathic, often associated with DM
  - usually resolves spontaneously in 9-18 mo
- secondary adhesive capsulitis
  - due to prolonged immobilization
  - shoulder-hand syndrome: CRPS/RSD characterized by arm and shoulder pain, decreased motion, and diffuse swelling
  - following MI, stroke, shoulder trauma
  - poorer outcomes

Stages of Adhesive Capsulitis
1. Freezing phase: gradual onset, diffuse pain (lasts 6-9 mo)
2. Frozen phase: decreased ROM impacts function (lasts 4-9 mo)
3. Thawing phase: gradual return of motion (lasts 5-26 mo)

Clinical Features
- gradual onset (weeks to months) of diffuse shoulder pain with:
  - decreased active AND passive ROM
  - pain worse at night and often prevents sleeping on affected side
  - increased stiffness as pain subsides: continues for 6-12 mo after pain has disappeared

Investigations
- x-ray: AP (neutral, internal/external rotation), scapular Y, and axillary views of the shoulder
  - may be normal, or may show demineralization from disease

Treatment
- freezing phase
  - maintenance of active and passive ROM (physiotherapy)
  - NSAIDs and steroid injections if limited by pain
- thawing phase
  - aggressive physiotherapy, possible manipulation under anesthesia and early physiotherapy
  - arthroscopy for debridement/decompression

Conditions Associated with an Increased Incidence of Adhesive Capsulitis
- Prolonged immobilization (most significant)
- Female gender
- Age >49
- DM (5x)
- Cervical disc disease
- Hyperthyroidism
- Stroke
- MI
- Trauma and surgery
- Autoimmune disease

Humerus

Proximal Humeral Fracture

Mechanism
- young: high energy trauma (MVC)
- elderly: FOOSH from standing height in osteoporotic individuals

Clinical Features
- proximal humeral tenderness, deformity with severe fracture, swelling, painful ROM, bruising extends down arm and chest
- physical exam usually reveals diminished forward elevation, with or without disuse atrophy of deltoid and periscapular musculature

Investigations
- test axillary nerve function (deltoid contraction and skin over deltoid)
- x-rays: AP, trans-scapular, and axillary views of the shoulder are essential
- CT scan: to evaluate for tuberosity or articular involvement and fracture displacement, and if the diagnosis of non-union is unclear

Neer Classification
Based on 4 parts of humerus and displacement of fragment (a fracture part is considered displaced if angulation is >45° or displacement is >1 cm)
- Greater tuberosity
- Lesser tuberosity
- Humeral head
- Shaft

One-part fracture: any of the 4 parts with none displaced
Two-part fracture: any of the 4 parts with 1 displaced
Three-part fracture: displaced fracture of surgical neck + displaced greater tuberosity or lesser tuberosity
Four-part fracture: displaced fracture of surgical neck + both tuberosities

Classification
- Neer classification is based on 4 fracture locations or 'parts'
- displaced: displacement >1 cm and/or angulation >45°
- the Neer system regards the number of displaced fractures, not the fracture line, in determining classification
- ± dislocated/subluxed humeral head from glenoid

Treatment
- assess for and treat osteoporosis if needed
- non-operative
  - nondisplaced and minimally displaced (85% of patients): broad arm sling immobilization, begin ROM within 14 d to prevent stiffness
  - most displaced fractures in low-demand elderly patients
- operative
  - ORIF (anatomic neck fractures, displaced, associated irreducible glenohumeral joint dislocation) or IM nail (surgical neck)
  - hemiarthroplasty or reverse TSA may be necessary, especially in elderly
  - minimally invasive percutaneous pinning and intramedullary nail fixation are indicated in rare instances

Specific Complications (see *General Fracture Complications, OR7*)
- AVN, nerve palsy (45%; typically axillary nerve), malunion, post-traumatic arthritis, persistent pain and weakness, frozen shoulder

Humeral Shaft Fracture

Mechanism
- young: high energy trauma (direct blows/MVC)
- elderly: FOOSH, twisting injuries, metastases

Clinical Features
- pain, swelling, weakness ± shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment: look for drop wrist, sensory impairment in dorsum of hand

Investigations
- x-ray: AP and lateral views of the humerus, including the shoulder and elbow joints

Treatment
- in general, humeral shaft fractures are treated non-operatively
- non-operative
  - ± reduction; can accept deformity due to compensatory ROM of shoulder
  - hanging cast (weight of arm in cast provides traction across fracture site) with collar and cuff sling immobilization until swelling subsides, then Sarmiento functional brace, followed by ROM
- operative
  - indications: see *NO CAST sidebar, OR6*, pathological fracture, "floating elbow" (simultaneous unstable humeral and forearm fractures)
  - ORIF: plating (most common), IM rod insertion, external fixation (rare)

Specific Complications (see *General Fracture Complications, OR7*)
- failure of functional bracing (seen in up to 30% of patients)
- radial nerve palsy: expect spontaneous recovery in 3-4 mo, otherwise send for EMG
- non-union: most frequently seen in middle 1/3
- decreased ROM
- compartment syndrome

Distal Humeral Fracture

Mechanism
- young: high energy trauma (MVC)
- elderly: lower energy falls in patients with osteoporotic bone

Clinical Features
- elbow pain and swelling
- assess brachial artery (ecchymosis over anteromedial forearm is suggestive of brachial artery injury)

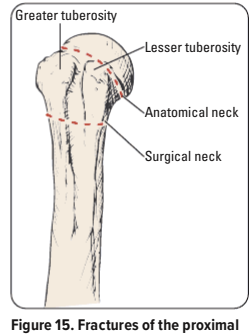


Figure 15. Fractures of the proximal humerus

Acceptable Humeral Shaft Deformities for Non-Operative Treatment
<20° anterior angulation
<30° varus angulation
<3 cm of shortening

Risk of radial nerve and brachial artery injury

The anterior humeral line refers to an imaginary line drawn along the anterior surface of the humeral cortex that passes through the middle third of the capitellum when extended inferiorly. In subtle supracondylar fractures, the anterior humeral line is disrupted, typically passing through the anterior third of the capitellum

Investigations
- x-ray: AP and lateral views of the humerus and elbow
- CT scan: helpful when suspecting shear fracture of capitulum or trochlea, and for preoperative planning
- assess NVS: radial, ulnar, and median nerve

Classification
- supracondylar, distal single column, distal bicolumnar, and coronal shear fractures

Treatment
- goal is to restore a functional ROM of at least 30-130° flexion (unsatisfactory outcomes in 25%)
- non-operative (pediatric patients and elderly patients with medical comorbidities)
  - cast immobilization (in supination for lateral condyle fracture; pronation for medial condyle fractures): short immobilization and early range of motion
- operative
  - indications: displaced, supracondylar, bicolumnar
  - closed reduction and percutaneous pinning (children); ORIF; total elbow arthroplasty (complex bicolumnar in elderly)
  - adult fractures are almost always treated operatively due to risk of elbow stiffness with non-operative management

Elbow

Supracondylar Fracture

- subclass of distal humerus fracture: extra-articular, fracture proximal to capitulum and trochlea, usually transverse
- most common in pediatric population (peak age ~7 yr), rarely seen in adults
- AIN (median nerve) injury commonly associated with extension type

Mechanism
- >96% are extension injuries via FOOSH (e.g. fall off monkey bars); <4% are flexion injuries

Clinical Features
- pain, swelling, point tenderness
- neurovascular injury: median and radial nerves, radial artery

Investigations
- x-ray: AP and lateral views of the elbow
  - disruption of anterior humeral line suggests supracondylar fracture
  - fat pad sign: a sign of effusion and can be indicative of occult fracture
  - assess NVS: median and radial nerves, radial artery

Treatment
- non-operative
  - nondisplaced (paediatric): closed reduction with long arm plaster slab in 90° flexion x 3 wk
- operative
  - indications: see *NO CAST sidebar, OR6*; displaced >50%, vascular injury, open fracture
  - requires closed reduction plus percutaneous pinning followed by limb cast with elbow flexed <90°
  - in adults, ORIF is necessary

Specific Complications (see *General Fracture Complications, OR7*)
- stiffness is most common
- brachial artery injury (kinking can occur if displaced fracture), median or ulnar nerve injury, compartment syndrome (leads to Volkmann's ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)

Three Joints at the Elbow
Humeroradial joint
Humeroulnar joint
Radioulnar joint

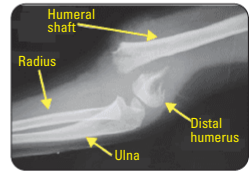


Figure 16. X-ray of transverse displaced supracondylar fracture of humerus with elbow dislocation

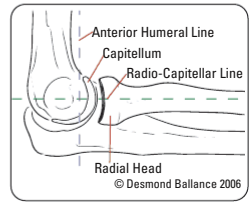


Figure 17. Lateral view of elbow

Capitellum moves posteriorly to the anterior humeral line in extension type fractures and anteriorly in flexion type fractures

Radial Head Fracture

- a common fracture of the upper limb in young adults (85% occur between 30-60 yr)

Mechanism
- FOOSH with elbow extended and forearm pronated

Clinical Features
- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, ± mechanical block to forearm pronation and supination
- pain on pronation/supination

Investigations
- x-ray: AP and lateral views of the elbow
  - enlarged anterior fat pad ("sail sign") or the presence of a posterior fat pad on lateral view indicates effusion, which could occur with occult radial head fractures

Table 12. Classification and Treatment of Radial Head Fractures

Mason Class	Radiographic Description	Treatment
1	Nondisplaced fracture (≤ 2 mm)	Elbow slab or sling x 3-5 d with early ROM
2	Displaced fracture (>2 mm)	ORIF if: angulation >30°, involves ≥1/3 of the radial head, or if ≥3 mm of joint incongruity exists, block to forearm rotation
3	Comminuted fracture	Radial head excision ± prosthesis (if ORIF not feasible)
4	Comminuted fracture with posterior elbow dislocation	Radial head ORIF or radial head excision with prosthesis

Treatment
- ORIF remains the gold standard in management
- arthroscopic repair can be considered: offers improved visualization and enhances soft tissue preservation of the joint

Specific Complications (see *General Fracture Complications, OR7*)
- myositis ossificans – calcification of muscle
- recurrent instability (if MCL injured and radial head excised)

Terrible Triad
Radial head fracture
Coronoid fracture
Elbow dislocation

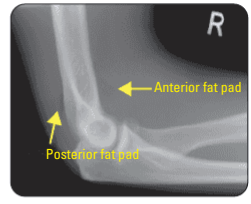


Figure 18. Lateral x-ray of elbow with effusion ("sail sign")

To avoid stiffness, do not immobilize elbow joint >2-3 wk

Olecranon Fracture

Mechanism
- direct blow: fall onto point of elbow (posterior aspect)
- indirect blow: FOOSH (typically transverse/oblique fracture)

Clinical Features
- localized pain, palpable defect
- ± loss of active extension due to avulsion of triceps tendon

Investigations
- x-ray: AP and lateral (require true lateral to determine fracture pattern)

Treatment
- non-operative
  - non-displaced (<2 mm, stable): cast x 2-3 wk (elbow in 90° flexion, often in full elbow extension), then gentle ROM
- operative
  - displaced ± non-intact extensor mechanism

Elbow Dislocation

- third most common joint dislocation after shoulder and patella
- simple: dislocation with no associated features
- complex: dislocation with associate features (fracture along with anterior capsule and/or collateral ligaments disrupted)

Mechanism
- elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion
- usually the radius and ulna are dislocated together, alternatively the radial head dislocates in isolation and the ulna is fractured (see *Monteggia Fracture, OR22*)
- 80% are posterior/posterolateral, anterior are rare and usually devastating

Clinical Features
- elbow pain, swelling, deformity
- flexion contracture
- ± absent radial or ulnar pulses

Investigations
- x-ray: AP and lateral views of the elbow
- assess NVS: brachial artery, median, and ulnar nerves

Treatment
- non-operative
  - closed reduction under conscious sedation (post-reduction x-rays required)
  - Parvin's method: patient lies prone with arm hanging down; apply gentle traction downwards on wrist; as olecranon slips distally, gently lift up the arm at elbow to reduce joint
  - long-arm splint with forearm in neutral rotation and elbow in 90° flexion
  - early ROM (<2 wk)
- operative
  - indications: complex fracture dislocation or persistent instability after closed reduction
  - ORIF

Specific Complications (see *General Fracture Complications, OR7*)
- stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture
- recurrent instability uncommon

Elbow Dislocation
The radio-capitellar line refers to an imaginary line along the longitudinal axis of the radial neck that passes through the centre of the capitellum, regardless of the degree of elbow flexion. If the radio-capitellar line does not pass through the centre of the capitellum a dislocation should be suspected

Epicondylitis

- lateral epicondylitis = "tennis elbow," inflammation of the common extensor tendon as it inserts into the lateral epicondyle
- medial epicondylitis = "golfer's elbow," inflammation of the common flexor tendon as it inserts into the medial epicondyle

Tennis Elbow = la**T**eral epicondylitis; pain associated with ex**T**ension of wrist

Mechanism
- repeated or sustained contraction of the forearm muscles/chronic overuse

Clinical Features
- point tenderness over humeral epicondyle and/or distal to it over forearm musculature
- pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
- generally a self-limited condition, but may take 6-18 mo to resolve

Treatment
- non-operative (very good outcomes)
  - rest, ice, NSAIDs
  - use brace/strap
  - physiotherapy, stretching, and strengthening
  - activity modification/ergonomics
  - corticosteroid injection
- operative
  - indication: failed 6-12 mo conservative therapy
  - percutaneous or open release of common tendon from epicondyle

Elbow Joint Injection
Inject at the centre of the triangle formed by the lateral epicondyle, radial head, and olecranon

Forearm

Radius and Ulna Shaft Fractures

Mechanism
- high-energy direct or indirect (MVA, fall from height, sports) trauma
- fractures usually accompanied by displacement due to high energy mechanism

Clinical Features
- deformity, pain, swelling
- loss of function in hand and forearm

Investigations
- x-ray: AP and lateral of forearm ± oblique of elbow and wrist
- CT if fracture is close to joint

Treatment
- goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
- ORIF with plates and screws; closed reduction with immobilization usually yields poor results for displaced forearm fractures (except in children)

Specific Complications (see *General Fracture Complications, OR7*)
- compartment syndrome
- soft tissue contracture resulting in limited forearm rotation – surgical release of tissue may be warranted

Monteggia Fracture

- fracture of the proximal ulna with radial head dislocation and proximal radioulnar joint injury
- more common and better prognosis in the pediatric age group when compared to adults

Mechanism
- direct blow to the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

Clinical Features
- pain, swelling, decreased rotation of forearm ± palpable lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

Investigations
- x-ray: AP and lateral views of the elbow, wrist, and forearm

Treatment
- adults (if stable): splint and early postoperative ROM if elbow completely stable, otherwise immobilization in plaster with elbow flexed for 2-3 wk
- adults (if unstable): ORIF of ulna with indirect reduction of radiocapitellar joint in 90% of patients (open reduction of radiocapitellar joint if unsuccessful)
- pediatrics: attempt closed reduction and immobilization in plaster with elbow flexed for Bado Type I-III, surgery for Type IV

Specific Complications (see *General Fracture Complications, OR7*)
- PIN injury: most common nerve injury; observe for 3 mo as most resolve spontaneously
- radial head instability/redislocation
- radioulnar synostosis

Nightstick Fracture

- isolated fracture of ulna without dislocation of radial head

Mechanism
- direct downward blow to upward block forearm (e.g. holding arm up to protect face)

Treatment
- non-operative
  - indication: non-displaced
  - below elbow cast (x 10 d), followed by forearm brace (~8 wk)
- operative
  - indication: significantly displaced
  - ORIF if >50% shaft displacement or >10° angulation

Galeazzi Fracture

- fracture of the distal radial shaft with disruption of the DRUJ
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis

Mechanism
- FOOSH with axial loading of pronated forearm or direct wrist trauma
- forceful axial loading of radial shaft (e.g. direct trauma to distal 1/3 of radius)

Clinical Features
- pain, swelling, deformity, and point tenderness at fracture site

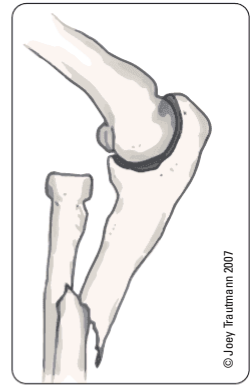


Figure 19. Monteggia fracture

In all isolated ulna fractures, assess proximal radius to rule out a Monteggia fracture

Bado Type Classification of Monteggia Fractures
Based on the direction of displacement of the dislocated radial head, generally the same direction as the apex of the ulnar fracture
Type I: anterior dislocation of radial head and proximal/middle third ulnar fracture (60%)
Type II: posterior dislocation of radial head and proximal/middle third ulnar fracture (15%)
Type III: lateral dislocation of radial head and metaphyseal ulnar fracture (20%)
Type IV – combined: proximal fracture of the ulna and radius, dislocation of the radial head in any direction (<5%)

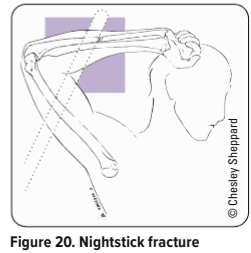


Figure 20. Nightstick fracture

Monteggia vs. Galeazzi Fractures
Remember the mnemonic "**MUGGER**":
Monteggia
Ulnar fracture
Galeazz
Radial fracture

Investigations
- x-ray: AP, and lateral views of the elbow, wrist, and forearm
  - shortening of distal radius >5 mm relative to the distal ulna
  - widening of the DRUJ space on AP
  - dislocation of radius with respect to ulna on true lateral

Treatment
- all cases are operative ("fracture of necessity")
  - ORIF of radius; afterwards, assess DRUJ stability by balloting distal ulna relative to distal radius
  - if DRUJ is stable and reduced, splint for 10-14 d with early ROM encouraged
  - if DRUJ is unstable, ORIF or percutaneous pinning with long arm cast in supination x 2-3 wk

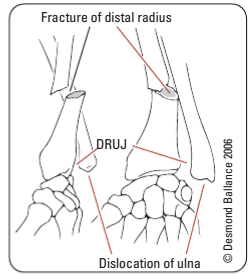


Figure 21. Galeazzi fracture

Wrist

Colles' Fracture

- extra-articular transverse distal radius fracture (~2 cm proximal to the radiocarpal joint) with dorsal displacement ± ulnar styloid fracture
- most common fracture in those >40 yr, especially in women and those with osteoporotic bone

Mechanism
- FOOSH

Clinical Features
- "dinner fork" deformity
- swelling, ecchymosis, tenderness

Investigations
- x-ray: AP and lateral ± oblique views of wrist

Treatment
- goal is to restore radial height (13 mm), radial inclination (23°), volar tilt (11°), as well as DRUJ stability and useful forearm rotation
- non-operative
  - hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
  - closed reduction: traction with extension (exaggerate injury); traction with ulnar deviation, pronation, flexion of distal fragment (not at wrist)"
  - dorsal slab/below elbow cast for 5-6 wk
  - obtain post-reduction films immediately; repeat reduction if necessary
  - x-ray at 1 wk, 3 wk, and at cessation of immobilization to ensure reduction is maintained
- operative
  - indication: failed closed reduction, or loss of reduction
  - percutaneous pinning, external fixation, or ORIF

Indications for Direct Surgical Management of Colles' Fracture
- Displaced intra-articular fracture
- Comminuted
- Severe osteoporosis
- Dorsal angulation >5° or volar tilt >20°
- >5 mm radial shortening

Features of Inadequate Closed Reduction that Require ORIF
- Radial shortening >3 mm or
- Dorsal tilt >10° or
- Intra-articular displacement/step-off >2 mm

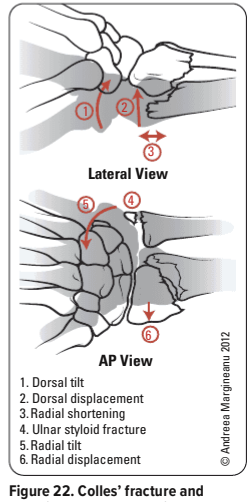


Figure 22. Colles' fracture and associated bony deformity

Smith's Fracture

- volar displacement of the distal radius (i.e. reverse Colles' fracture)

Mechanism
- fall onto the back of the flexed hand

Investigations
- x-ray: AP and lateral ± oblique views of wrist

Treatment
- if non-displaced/stable: closed reduction and splinting in wrist extension with hematoma or regional nerve block; long arm cast in supination x6 wk
- if displaced/unstable: ORIF

Complications of Wrist Fractures

- most common complications are poor grip strength, stiffness, and radial shortening
- distal radius fractures in individuals <40 yr of age are frequently high energy/comminuted and are more likely to require ORIF
- 80% have normal function in 6-12 mo

Table 13. Early and Late Complications of Wrist Fractures

Early	Late
Difficult reduction ± loss of reduction	Malunion, radial shortening
Compartment syndrome	Painful wrist secondary to ulnar prominence
Extensor pollicis longus tendon rupture	Frozen shoulder ("shoulder-hand syndrome")
Acute carpal tunnel syndrome	Post-traumatic arthritis
Finger swelling with venous block	Carpal tunnel syndrome
Complications of a tight cast/splint	CRPS/RSD

Scaphoid Fracture

Epidemiology
- most common carpal bone injured
- common in young men; not common in children or in patients beyond middle age
- may be associated with other carpal or wrist injuries (e.g. Colles' fracture)

Mechanism
- FOOSH: impaction of scaphoid on distal radius, most commonly resulting in a transverse fracture through the waist (65%), distal (10%), or proximal (25%) scaphoid

Clinical Features
- pain with resisted pronation
- tenderness in the anatomical "snuff box," over scaphoid tubercle, and pain with long axis compression into scaphoid
- usually non-displaced

Investigations
- x-ray: AP, lateral, and scaphoid views with wrist extension and ulnar deviation
- ± CT or MRI: detect occult fracture and prevent AVN
- bone scan rarely used
  - note: a fracture may not be radiologically evident up to 2 wk after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 wk later to rule out a fracture; if x-ray still negative, order CT or MRI

Treatment
- early treatment critical for improving outcomes
- non-operative
  - non-displaced (<1 mm displacement/<15° angulation): long-arm thumb spica cast x 4 wk, then short arm cast until radiographic evidence of healing is seen (2-3 mo)
- operative
  - displaced: ORIF with headless/countersink compression screw is the mainstay treatment

Specific Complications (see *General Fracture Complications, OR7*)
- most common: nonunion/malunion (use bone graft from iliac crest or distal radius with fixation to heal)
- AVN of the proximal fragment
- delayed union (recommend surgical fixation)
- scaphoid nonunion advanced collapse (SNAC) – chronic nonunion leading to advanced collapse and arthritis of wrist

Prognosis
- proximal pole: proximal fifth fracture, AVN rate 100%; proximal third fracture: AVN rate 33%
- waist: middle of the scaphoid fractures have healing rates of 80-90%
- distal pole: distal third fractures have healing rates close to 100%

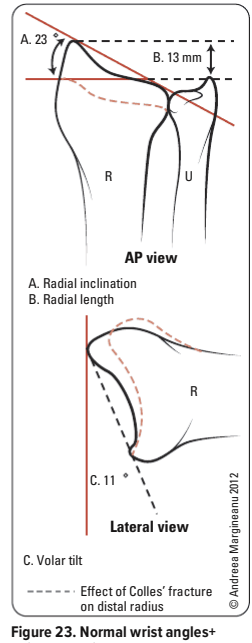


Figure 23. Normal wrist angles+ wrist angles in Colles' fracture
Note the relative shortening of the radius relative to the ulna on AP view in Colles' fracture

Scaphoid Fracture Special Tests
Tender snuff box: 100% sensitivity, but 29% specific, as it is also positive with many other injuries of radial aspect of wrist with FOOSH

The proximal pole of the scaphoid receives as much as 100% of its arterial blood supply from the radial artery that enters at the distal pole. A fracture through the proximal third disrupts this blood supply and results in a high incidence of AVN/nonunion

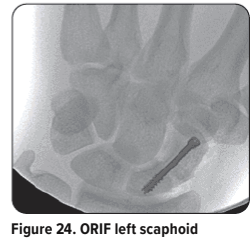


Figure 24. ORIF left scaphoid

Hand

- see Plastic Surgery, PL24

Spine

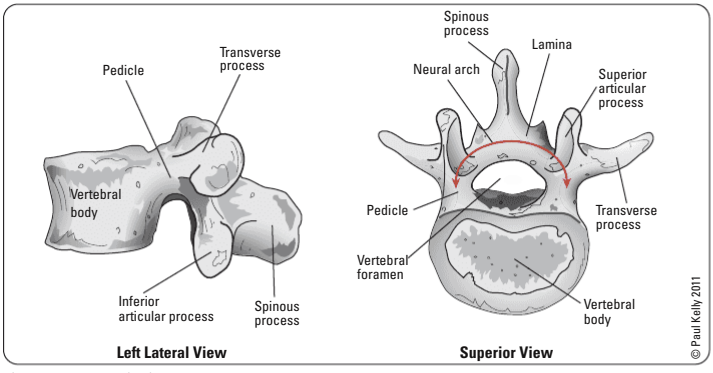


Figure 27. Schematic diagram of vertebral anatomy
Adapted from: Moore KL, Agur AMR. Essential Clinical Anatomy, 3rd ed. Philadelphia: Lippincott Williams and Wilkins, 2007. p274

Fractures of the Spine

- see Neurosurgery, NS39

Cervical Spine

General Principles

- C1 (atlas): no vertebral body, no spinous process
- C2 (axis): odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
- nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra), C8 nerve root exits below C7 vertebra
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord

Special Testing

- compression test: pressure on head worsens radicular pain
- distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain
- Lhermitte Sign: electric shock sensation radiating to back upon forward flexion of the neck, some etiologies include multiple sclerosis, cervical myelopathy, and B12 deficiency
- occiput-wall distance (OWD): patient stands against a wall with erect posture and distance between the occiput and the wall is measured, value greater than 2 cm is abnormal, indicative of thoracic hyper-kyphosis

Table 14. Cervical Radiculopathy/Neuropathy

Root	C5	C6	C7	C8
Motor	Deltoid Biceps	Biceps Brachioradialis Wrist extension	Triceps Wrist flexion Finger extension	Interossei Digital flexors
Sensory	Axillary nerve (patch over lateral deltoid)	Thumb	Index and middle finger	Ring and little finger
Reflex	Biceps	Biceps Brachioradialis	Triceps	Finger jerk

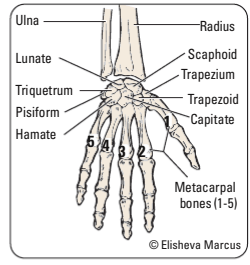


Figure 25. Carpal bones

Order of Carpal Bones
So **L**ong **T**o **P**inky, **H**ere **C**omes **T**he **T**humb
Proximal Row: **S**caphoid, **L**unate, **T**riquetrum, **P**isiform (Lateral to Medial)
Distal Row: **H**amate, **C**apitate, **T**rapezoid,**T**rapezium (Medial to Lateral)

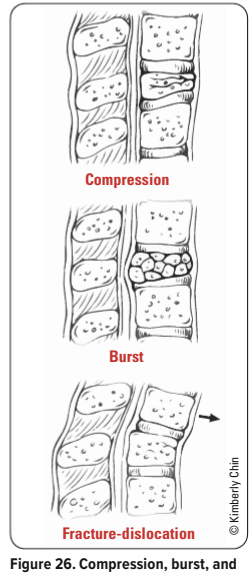


Figure 26. Compression, burst, and dislocation fractures of the spine

X-Rays for C-Spine
- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- lateral
  - vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
  - angulation: between adjacent vertebral bodies (>11° is abnormal)
  - disc or facet joint widening
  - anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
- oblique: evaluate pedicles and intervertebral foramen
- ± swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
- ± lateral flexion/extension view: evaluate subluxation of cervical vertebrae

Differential Diagnosis of C-Spine Pain
- neck muscle strain, cervical spondylosis, cervical stenosis, RA (spondylitis), traumatic injury, whiplash, myofascial pain syndrome, acute discogenic nerve root entrapment, infection, fracture, neoplasm, pain from soft tissue structure

C-SPINE INJURY
- see Neurosurgery, NS38

Thoracolumbar Spine

General Principles
- spinal cord terminates at conus medullaris (L1/2)
- individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)

Special Tests
- straight leg raise: passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down posterior/lateral leg to knee ± into foot
- Lasegue maneuver: dorsiflexion of foot during straight leg raise makes symptoms worse, or if leg is less elevated, dorsiflexion will bring on symptoms
- femoral stretch test: with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular symptoms of unilateral pain in anterior thigh

Table 15. Lumbar Radiculopathy/Neuropathy

Root	L4	L5	S1
Motor	Quadriceps (knee extension + hip flexion) Tibialis anterior (ankle inversion + dorsiflexion)	Extensor hallucis longus Gluteus medius (hip abduction)	Peroneus longus + brevis (ankle eversion) Gastrocnemius + soleus (plantar flexion)
Sensory	Medial malleolus	1st dorsal webspace and lateral leg	Lateral foot
Screening Test	Squat and rise	Heel walking	Walking on toes
Reflex	Knee (patellar)	Medial hamstring*	Ankle (Achilles)
Test	Femoral stretch	Straight leg raise	Straight leg raise

Differential Diagnosis of Back Pain
1. mechanical or nerve compression (>90%)
   - degenerative (disc, facet, ligament)
   - nerve root compression (e.g. disc herniation)
   - spinal stenosis (congenital, osteophyte, central disc)
2. others (<10%)
   - neoplastic (primary, metastatic, multiple myeloma)
   - infectious (osteomyelitis, TB)
   - metabolic (osteoporosis)
   - traumatic fracture (compression, distraction, translation, rotation)
   - spondyloarthropathies (ankylosing spondylitis)
   - referred (aorta, renal, ureter, pancreas)

DEGENERATIVE DISC DISEASE
- loss of vertebral disc height with age resulting in:
  - bulging and tears of annulus fibrosus
  - change in alignment of facet joints
  - osteophyte formation

Mechanism
- compression and dehydration of disc material over time with age

Clinical Features
- axial back pain
- pain worse with axial loading and flexion
- negative straight leg raise

Investigations
- x-ray, MRI, provocative discography
- imaging only indicated if symptoms persist greater than 6 wk or if red flag symptoms are present

Treatment
- non-operative
  - staying active with modified activity
  - back strengthening
  - NSAIDs
  - do NOT treat with opioids; no proven efficacy of spinal traction or manipulation
- operative – rarely indicated
  - decompression ± fusion (in cases of severe or progressive neurological deficit; refractory cases with impaired quality of life)

SPINAL STENOSIS
- narrowing of spinal canal
- congenital (idiopathic, osteopetrosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylosis, Paget's disease, trauma)

Clinical Features
- ± bilateral back and leg pain
- neurogenic claudication
- ± motor weakness

Investigations
- CT/MRI reveals narrowing of spinal canal

Treatment
- non-operative
  - physiotherapy (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
- operative
  - indication: non-operative failure >6 mo
  - decompressive surgery

Table 16. Differentiating Claudication

	Neurogenic	Vascular
Aggravation	With standing/walking Walking distance variable	Walking/exercise (reproducible)
Alleviation	Change in position (usually flexion, sitting, lying down)	Stop walking/exercise
Time	Relief in ~10 min	Relief in ~2 min

MECHANICAL BACK PAIN
- back dominant pain that does not involve nerve impingement

Clinical Features
- dull backache aggravated by activity and prolonged standing (or sitting, depending on cause and pathology)
- morning stiffness (e.g. if facet OA)
- no neurological signs

Treatment
- symptomatic (analgesics, physiotherapy, weight loss, and exercise program)
- prognosis: symptoms may resolve in 4-6 wk, others become chronic

LUMBAR DISC HERNIATION
- tear in annulus fibrosus allows protrusion of nucleus pulposus, causing either a central, posterolateral, or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
- M:F=3:1
- only 5% become symptomatic
- usually a history of flexion-type injury

Clinical Features
- back dominant pain (central herniation) or leg dominant pain (lateral herniation)
- tenderness between spinous processes at affected level
- muscle spasm ± loss of normal lumbar lordosis

Cauda equina syndrome and ruptured aortic aneurysms are causes of low back pain that are considered surgical emergencies

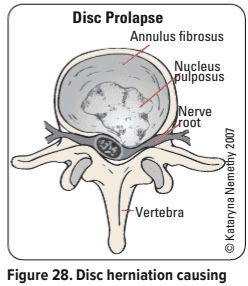


Figure 28. Disc herniation causing nerve root compression

- neurological disturbance is segmental and varies with level of central herniation
  - motor weakness (L4, L5, S1)
  - diminished reflexes (L4, S1)
  - diminished sensation (L4, L5, S1)
- positive straight leg raise
- positive contralateral SLR
- positive Lasegue and Bowstring sign
- cauda equina syndrome (present in 1-10%): surgical emergency

Neurogenic claudication is position dependent; vascular claudication is exercise dependent

Investigations
- x-ray, MRI, consider a post-void residual volume to check for urinary retention; post-void >100 mL should heighten suspicion for cauda equina syndrome

MRI abnormalities (e.g. spinal stenosis, disc herniation) are quite common in both asymptomatic and symptomatic individuals and are not necessarily an indication for intervention without clinical correlation

Treatment
- non-operative
  - symptomatic
    - extension protocol physiotherapy program
    - NSAIDs
- operative
  - indication: progressive neurological deficit, failure of symptoms to resolve within 3 mo, or cauda equina syndrome due to central disc herniation
  - surgical discectomy
- prognosis
  - 90% of patients improve in 3 mo with non-operative treatment

Table 17. Types of Low Back Pain

	Mechanical Back Pain		Direct Nerve Root Compression	
	Disc Origin	**Facet Origin**	**Spinal Stenosis**	**Root Compression**
Pain Dominance	Back	Back	Leg	Leg
Aggravation	Flexion	Extension, standing, walking	Exercise, extension, walking, standing	Flexion
Onset	Gradual	More sudden	Congenital or acquired	Acute leg ± back pain
Duration	Long (weeks, months)	Shorter (days, weeks)	Acute or chronic history (weeks to months)	Constant and severe pain, lasting weeks)
Treatment	Relief of strain, physiotherapy and exercise, weight loss, NSAIDs, acetaminophen	Relief of strain, physiotherapy and exercise, weight loss, NSAIDs, acetaminophen	Relief of strain, physiotherapy (flexion back program), surgical decompression if progressive or severe deficit, NSAIDs, acetaminophen	Relief of strain, physiotherapy (extension back program for disc herniation), surgical decompression if progressive or severe deficit, NSAIDs, acetaminophen

Red Flags for

BACK PAIN
Bowel or bladder dysfunction
Anesthesia (saddle)
Constitutional symptoms/malignancy
Khronic disease
Paresthesias
Age >50 yr
IV drug use
Neuromotor deficits

Sciatica

Most common symptom of radiculopathy (L4-S3)

Leg dominant, constant, burning pain

Pain radiates down leg ± foot

Most common cause = disc herniation

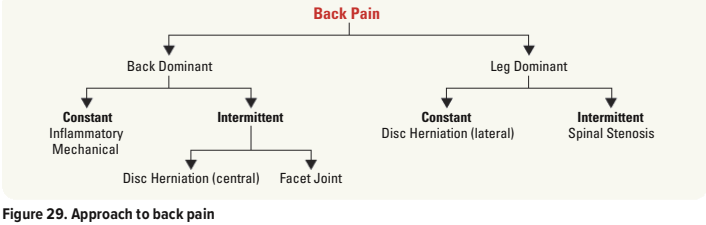


Figure 29. Approach to back pain

SPONDYLOLYSIS

Definition
- defect in the pars interarticularis with no movement of the vertebral bodies

Mechanism
- trauma: gymnasts, weightlifters, backpackers, loggers, labourers

Clinical Features
- activity-related back pain, pain with unilateral extension (Michelis' test)

Investigations
- oblique x-ray: "collar" break in the "Scottie dog's" neck
- bone scan
- CT scan

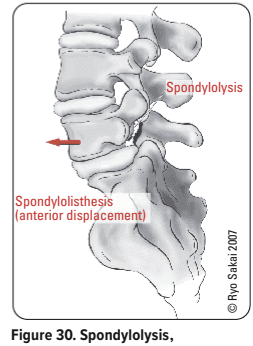


Figure 30. Spondylolysis, Spondylolisthesis

Treatment
- non-operative
  - activity restriction, brace, stretching exercise

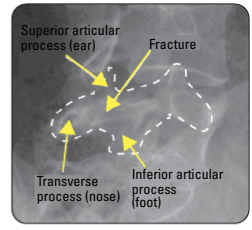


Figure 31. "Scottie dog" fracture

ADULT ISTHMIC SPONDYLOLISTHESIS

Definition
- defect in pars interarticularis causing a forward translation or slippage of one vertebra on another, usually at L5-S1, less commonly at L4-5

Mechanism
- degenerative (adults), traumatic, pathological, teratogenic

Clinical Features
- lower back pain radiating to buttocks relieved with sitting
- neurogenic claudication
- L5 radiculopathy
- Meyerding Classification (percentage of slip)

Investigations
- x-ray (AP, lateral, oblique flexion-extension views), MRI

Treatment
- non-operative
  - activity restriction, bracing, NSAIDs
- operative

Table 18. Classification and Treatment of Spondylolisthesis

Class	Percentage of Slip	Treatment
1	0-25%	Symptomatic operative fusion only for intractable pain
2	25-50	Same as above
3	50-75	Decompression for spondylolisthesis and spinal fusion
4	75-100	Same as above
5	>100	Same as above

Specific Complications
- may present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

Pelvis

Pelvic Fracture

Mechanism
- young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- elderly: low energy trauma, fall from standing height
- lateral compression, vertical shear, or anteroposterior compression fractures

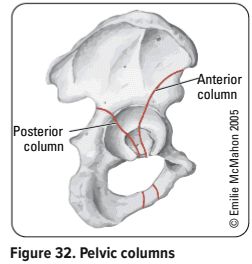


Figure 32. Pelvic columns

Clinical Features
- pain, inability to bear weight
- local swelling, tenderness
- abnormal lower extremity positioning: external rotation of one or both extremities, limb-length discrepancy
- pelvic instability

Investigations
- x-ray: AP pelvis, inlet and outlet views, Judet views (visualizes obturator and iliac oblique when acetabular fracture suspected)
  - 6 cardinal radiographic landmarks of the acetabulum: ilioischial line, iliopectineal line, teardrop, weight bearing roof, posterior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture (if stable)
  - may see contrast blush (indicating active bleeding)
- assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)
  - if involved, the fracture is considered an open fracture

Classification

Table 19. Tile Classification of Pelvic Fractures

Type	Stability	Description
A	Rotationally stable Vertically stable	A1: fracture not involving pelvic ring (i.e. avulsion or iliac wing fracture) A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture) A3: transverse sacral or coccygeal fracture
B	Rotationally unstable Vertically stable	B1: open book (external rotation) B2: lateral compression – ipsilateral B2-1: with anterior ring rotation/displacement through ipsilateral rami B2-2: with anterior ring rotation/displacement through non-ipsilateral rami (bucket-handle) B3: bilateral
C	Rotationally unstable Vertically unstable	C1: unilateral C1-1: iliac fracture C1-2: sacroiliac fracture-dislocation C1-3: sacral fracture C2: bilateral with 1 side type B and 1 side type C C3: bilateral both sides type C

Possible Radiological Findings
- Pubic rami fractures: superior/inferior
- Pubic symphysis diastasis: common in AP compression (N=5 mm)
- Sacral fractures: common in lateral compression
- SI joint diastasis: common in AP compression (N=1-4 mm)
- Disrupted anterior column (iliopectineal line) or posterior column (ilioischial line)
- "Teardrop" displacement: acetabular fracture
- Iliac, ischial avulsion fractures
- Displacement of the major fragment: superior (VS), open book (APC), bucket handle (LC)

Treatment
- ABCDEs
- emergency management
  - IV fluids/blood
  - pelvic binder/sheet
  - external fixation vs. emergent angiography/embolization
  - ± laparotomy (if FAST/DPL positive)
  - ± pre-peritoneal packing)
- non-operative treatment: protected WB
  - indication: stable fracture (e.g. elderly patient with fracture sustained in fall from standing)
- operative treatment: ORIF
- indications
  - unstable pelvic ring injury
  - symphysis diastasis >2.5 cm
  - open fracture

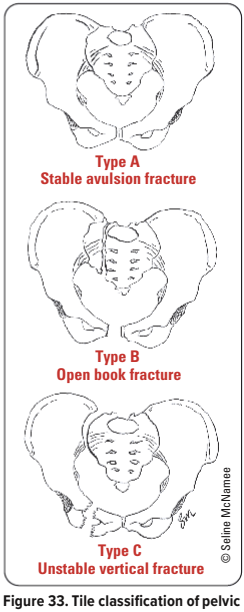


Figure 33. Tile classification of pelvic fractures

Specific Complications (see *General Fracture Complications, OR7*)
- hemorrhage (life-threatening)
- injury to rectum or urogenital structures
- obstetrical difficulties, sexual and voiding dysfunctions
- persistent SI joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high-risk of DVT/PE

Hip

Hip Dislocation

- full trauma survey (see Emergency Medicine, *Patient Assessment/Management, ER2*)
- examine for neurovascular injury prior to open or closed reduction
- high index of suspicion for associated injuries
- reduce hip dislocations within 6 h to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 wk post-reduction
- see *Hip Dislocation Post-Total Hip Arthroplasty, OR32*

Up to 50% of patients with hip dislocations suffer fractures elsewhere at the time of injury

ANTERIOR HIP DISLOCATION
- mechanism: posteriorly directed axial loading of the femur with hip widely abducted and externally rotated
- classified into inferior (flexion, abduction, external rotation) and superior (extension and external rotation)
- clinical features: shortened, abducted, externally rotated limb
- treatment
  - closed reduction under conscious sedation/GA
  - post-reduction CT to assess joint congruity

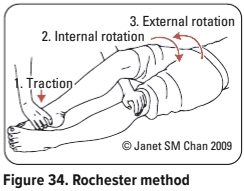


Figure 34. Rochester method

POSTERIOR HIP DISLOCATION

- most frequent type of hip dislocation (90%)
- mechanism: severe axial load to knee with hip flexed and adducted
  - e.g. knee into dashboard in MVC
- clinical features: shortened, adducted, internally rotated limb
- x-ray: affected femoral head will appear smaller than unaffected femoral head
- Thompson and Epstein classification – posterior dislocation:
  - I – with no or minor posterior acetabular wall fracture
  - II – with large posterior acetabular wall fracture
  - III – with comminuted acetabular fracture
  - IV – with acetabular floor fracture
  - V – with fracture of femoral head
- treatment
  - urgent closed reduction under conscious sedation/GA only if no associated femoral neck fracture or ipsilateral displacement
  - ORIF if unstable, intra-articular fragments, or significant displacement
  - post-reduction CT to assess joint congruity and fractures

COMPLICATIONS FOR ALL HIP DISLOCATIONS

- post-traumatic OA
- AVN of femoral head - risk increases with delay in reduction
- associated fractures (e.g. femoral head, neck, or shaft)
- sciatic nerve palsy in 25% (10% permanent)
- HO
- thromboembolism – DVT/PE
- hip instability and re-dislocation

Hip Fracture

General Features

- acute onset of hip pain after a fall
- unable to weight-bear
- shortened and externally-rotated leg
- painful ROM

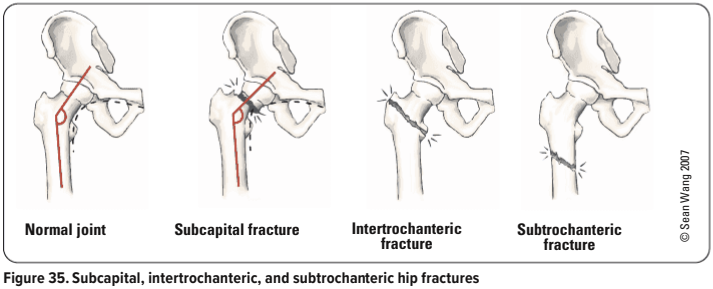


Figure 35. Subcapital, intertrochanteric, and subtrochanteric hip fractures

Table 20. Overview of Hip Fractures

Fracture Type	Definition	Mechanism	Investigations	Treatment	Complications
Femoral Neck (Subcapital)	Intracapsular	Young: MVC, fall from height Elderly: fall from standing, rotational force	X-Ray: AP hip, AP pelvis, cross table lateral hip	See *Table 21, OR32*	DVT, non-union, AVN, dislocation
Intertrochanteric Stable: intact posteromedial cortex Unstable: non-intact posteromedial cortex	Extracapsular fracture between the greater and lesser trochanters and transitional bone between the neck and shaft	Same as femoral neck fracture Direct or indirect force transmitted to the intertrochanteric area	X-Ray: AP hip, AP pelvis, cross table lateral hip	Closed reduction under fluoroscopy then dynamic hip screw or IM nail	DVT, varus displacement of proximal fragment, malrotation, non-union, failure of fixation device
Subtrochanteric	Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft	Young: high energy trauma Elderly: osteopenic bone + fall, pathological fracture	X-Ray: AP pelvis, AP/lateral hip and femur	Closed/open reduction under fluoroscopy, then IM nail	Malalignment, non-union, wound infection

X-Ray Features of Subcapital Hip Fractures

- Disruption of Shenton's line (a radiographic line drawn along the upper margin of the obturator foramen, extending along the inferomedial side of the femoral neck)
- Altered neck-shaft angle (normal is 120-130°)

DVT Prophylaxis in Hip Fractures

LMWH (i.e. enoxaparin 40 mg SC once daily), fondaparinux, low dose heparin on admission, do not give <12 h before surgery

Source: UpToDate - Prevention of venous thromboembolism in adult orthopedic surgical patients. Enoxaparin (Lovenox) US FDA approved product information https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020164s110lbl.pdf

AVN of Femoral Head

- Distal to proximal blood supply along femoral neck to head (medial and lateral femoral circumflex arteries)
- Susceptible to AVN if blood supply disrupted
- Etiology: femoral neck fracture, chronic systemic steroid use, SCFE, Legg-Calvé-Perthes, SLE, RA

Table 21. Garden Classification of Femoral Neck Fractures

Type	Displacement	Extent	Alignment	Trabeculae	Treatment
I	None	"Incomplete"	Valgus or neutral	Disrupted	Internal fixation to prevent displacement (valgus impacted fracture)
II	None	Complete	Neutral	Aligned	Internal fixation to prevent displacement
III	Partial	Complete	Varus	Disrupted	Young: ORIF Elderly: hemi-/total hip arthroplasty
IV	Complete	Complete	Varus	Disrupted	Young: ORIF Elderly: hemi-/total hip arthroplasty

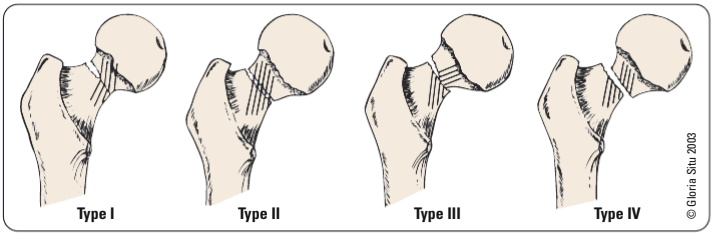


Figure 36. Garden classification of femoral neck fractures

Comparative Effectiveness of Pain Management Interventions for Hip Fracture: A Systematic Review
Ann Intern Med 2011;155(4):234-245
Purpose: To review the harms and benefits of various pharmacologic and non-pharmacological interventions for pain post-hip fracture.
Methods: Twenty-five databases were searched for randomized controlled trials, non-randomized controlled trials, and cohort studies investigating pain management techniques in older adults after acute hip fracture were eligible for inclusion.
Results: 83 studies were eligible for inclusion. Moderate-level evidence suggests nerve blockades are effective for acute pain management and reducing delirium. There is low-level evidence that preoperative traction does not improve acute pain. There is insufficient evidence to draw conclusions about the benefits/harms of other pain management interventions such as spinal anesthesia, acupressure, and transcutaneous electrical neurostimulation.
Conclusions: Nerve blockade seems to be effective in reducing acute pain after hip fracture. Insufficient data precludes conclusions about the relative benefits/harms of other pain management interventions post-hip fracture.

Arthritis of the Hip

Etiology
- OA, inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders, or septic arthritis

Clinical Features
- OA: pain (groin, medial thigh) and stiffness aggravated by activity, relieved with rest
- inflammatory RA: joint pain, morning stiffness >1 h, multiple joint swelling, hand nodules
- decreased ROM (internal rotation is usually lost first)
- crepitus
- leg length discrepancy (secondary to loss of cartilage and/or bone in affected joint)
- ± fixed flexion contracture leading to apparent limb shortening (Thomas test)
- ± Trendelenburg sign and/or gait (limp)

Investigations
- x-ray: WB views of affected joint
  - OA findings - **LOSS**: **L**oss of joint space, **O**steophytes**, S**ubchondral sclerosis, **S**ubchondral cysts
  - inflammatory (e.g. RA): osteopenia, periarticular erosions, concentric joint space narrowing
- blood work: ANA, RF

Treatment
- non-operative
  - weight loss, activity modification, physiotherapy, analgesics, anti-inflammatory medications, walking aids
- operative
  - indication: advanced disease with symptoms significantly affecting quality of life
  - realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
- complications with arthroplasty: component loosening, dislocation, HO, thromboembolism, infection, neurovascular injury, limb length discrepancy, persistent limp, periprosthetic fracture
- arthroplasty is standard of care in most patients with hip arthritis

Hip Dislocation Post-Total Hip Arthroplasty

- occurs in 1-4% of primary THA and 10-16% of revision THAs
- common indication for early revision
- risk factors: post-traumatic arthritis, revision surgery, substance use, cognitive impairment (dementia), spastic or neuromuscular disease, posterior surgical approach, spinal fusion

Mechanism
- flexion, adduction, and internal rotation (posterior dislocation), or extension and external rotation (anterior dislocation)

Investigations
- x-ray: AP pelvis, AP and lateral views of the hip

Treatment
- non-operative
  - closed reduction and immobilization
- operative
  - indication: recurrent dislocations, associated polyethylene wear, malalignment, hardware failure, or infection
  - revision THA
  - infected hip (infection can cause hip instability)

Complications
- sciatic nerve palsy in 25% (10% permanent)
- HO
- infection

DVT Prophylaxis in Elective THA
(continue 10-35 d postoperative)
DOACs (e.g. rivaroxaban), ASA, fondaparinux, low molecular weight heparin, or warfarin

Femur

Femoral Diaphysis Fracture

Mechanism
- high energy trauma (MVC, fall from height, gunshot wound)
  - pathologic as a result of malignancy, osteoporosis, bisphosphonate use
- in children, can result from low energy trauma (spiral fracture)
  - always consider the possibility of non-accidental trauma (child abuse)

Clinical Features
- shortened, externally rotated leg (if fracture displaced)
- inability to weight-bear
- often open injury, always a Gustilo III (see *Table 6, OR10*)
- Winquist and Hansen classification

It is important to rule out ipsilateral femoral neck fracture, as they occur in 2-6% of femoral diaphysis fractures and are reportedly missed in 19-31% of cases

Investigations
- x-ray: AP pelvis, AP and lateral views of the hip, femur, knee

Treatment
- non-operative (pediatric, uncommon in adults)
  - possible indication: non-displaced femoral shaft fractures in patients with significant comorbidities who are non-ambulatory
  - most femoral shaft fractures require fixation as this is a life-threatening injury
- operative
  - ORIF with anterograde IM nail (most common) or retrograde IM nail or with plate and screw fixation
  - external fixation may be used initially (e.g. unstable patients or polytrauma patients)
  - early mobilization and strengthening

Complications
- blood loss
- infection
- fat embolism leading to ARDS
- VTE
- malrotation, leg length discrepancy
- malunion/nonunion

Associated Injuries
- extensive soft tissue damage
- ipsilateral hip dislocation/fracture (2-6%)
- nerve injury

Distal Femoral Fracture

• fractures from articular surface to 5 cm above metaphyseal flare

Mechanism
• direct high energy force or axial loading (may occur due to fall from standing in osteoporotic patients)
• three types: extra articular, partial articular, complete articular

Clinical Features
• extreme pain worse with knee motion
• knee effusion (hemarthrosis)
• neurovascular deficits can occur with displaced fracture

Investigations
• x-ray: AP and lateral views
• ABI if diminished pulses or concern for vascular injury, angiography (ABI <0.9)
• CT: to evaluate the articular surface and degree of comminution

Treatment
• non-operative (uncommon)
  ▪ indication: non-displaced extra-articular fracture, poor surgical candidate
  ▪ hinged knee brace
• operative
  ▪ indication: displaced fracture, intra-articular fracture
• ORIF with plate or retrograde IM nail fixation
• knee arthroplasty with distal femoral replacement prosthesis (elderly, low demand patient with comminuted fracture)
• early mobilization

Specific Complications (see *General Fracture Complications, OR7*)
• vascular injury
• nerve injury
• angular deformities/malunion
• post-traumatic arthritis

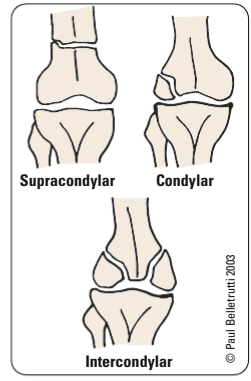


Figure 37. Distal femoral fractures

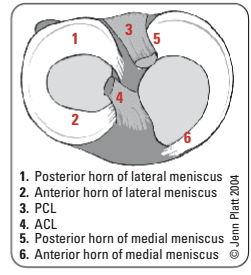


Figure 38. Diagram of the right tibial plateau

Knee

Evaluation of Knee

Common Complaints
• locking, instability, and swelling
  ▪ suggests intra-articular pathology such as a torn meniscus or cruciate ligament injury
• pseudo-locking: limited ROM without mechanical block
  ▪ muscle spasm after injury, arthritis
• painful, audible clicking
  ▪ torn meniscus, cartilage injury, or floating body

Special Tests of the Knee
• **anterior and posterior drawer tests** (*Figure 40, OR35*)
  ▪ demonstrates torn ACL and PCL, respectively
  ▪ knee flexed at 90°, foot immobilized, hamstrings relaxed
  ▪ anterior subluxation of the tibia (anterior drawer test), suggests ACL injury
  ▪ posterior subluxation of the tibia (posterior drawer test), suggests PCL injury
  ▪ anterior drawer test for ACL: 3.8 positive likelihood ratio, 0.30 negative likelihood ratio
  ▪ posterior drawer test for PCL: 16.2 positive likelihood ratio, 0.2 negative likelihood ratio
• **Lachman test**
  ▪ demonstrates torn ACL
  ▪ hold knee in 20-30° flexion, stabilizing the distal femur with one hand
  ▪ with contralateral hand, attempt to sublux tibia anteriorly on femur
  ▪ similar to anterior drawer test, more reliable due to less muscular stabilization
  ▪ for ACL: 25.0 positive likelihood ratio, 0.1 negative likelihood ratio
• **pivot shift sign**
  ▪ demonstrates torn ACL
  ▪ start with the knee in extension
  ▪ requires relaxed patient, best performed in patient under spinal or general anesthesia
  ▪ internally rotate foot, slowly flex knee while palpating and applying a valgus force
  ▪ if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the "pivot")

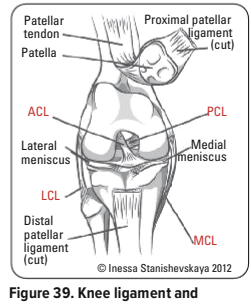


Figure 39. Knee ligament and anatomy

6 Degrees of Freedom of the Knee
- Flexion and extension
- External and internal rotation
- Varus and valgus angulation
- Anterior and posterior glide
- Medial and lateral shift
- Compression and distraction

On physical exam of the knee, do not forget to evaluate the hip

  - reverse pivot shift (start in flexion, externally rotate, apply valgus, and extend knee) suggests posterolateral corner injury
  - composite assessment for ACL: 25.0 positive likelihood ratio, 0.04 negative likelihood ratio
  - composite assessment for PCL: 21.0 positive likelihood ratio, 0.05 negative likelihood ratio
- **posterior sag sign**
  - suggests torn PCL
  - posterior tibial subluxation may lead to false positive anterior drawer sign
  - flex knees and hips to 90°, hold ankles and knees
  - view from the lateral aspect
  - visible posterior tibial sag when compared to uninjured knee suggests PCL injury
- **collateral ligament stress test (varus/valgus instability)**
  - palpate ligament for "opening" of joint space while testing
  - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
  - repeat tests with knee in 20° flexion to relax joint capsule
  - opening in 20° flexion suggests MCL injury (valgus force), LCL injury (varus force)
  - opening in 20° of flexion and full extension suggests MCL, cruciate, and joint capsule damage (valgus force)
- **tests for meniscal tear**
  - **joint line tenderness**
    - joint line pain when palpated
    - palpate medial and lateral joint line and observe patient for signs of pain
    - for meniscal tear: 0.9 positive likelihood ratio, 1.1 negative likelihood ratio
  - **crouch compression test**
    - joint line pain when squatting (anterior pain suggests patellofemoral pathology)
  - **McMurray's test**
    - with knee in flexion, palpate joint line for painful pop or click
    - lateral meniscus tear exam: internally rotate foot, apply varus stress, and extend knee
    - medial meniscus tear exam: externally rotate foot, apply valgus stress, and extend knee
    - for meniscal tear: 1.3 positive likelihood ratio, 0.8 negative likelihood ratio

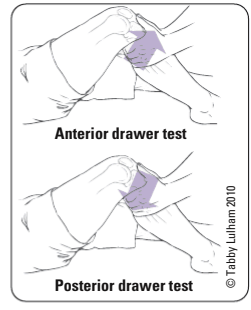


Figure 40. Anterior and posterior drawer test

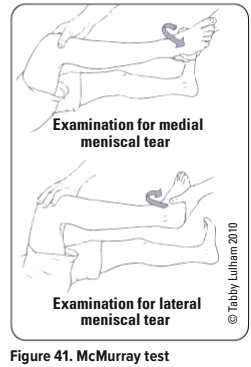


Figure 41. McMurray test

X-Rays

- AP standing, lateral
- skyline: tangential view with knees flexed at 45° to see patellofemoral joint
- 3-foot standing view: useful in evaluating leg length and varus/valgus alignment
- Ottawa Knee Rules (see Emergency Medicine, ER16)

Cruciate Ligament Tears

- ACL tear much more common than PCL tear

Table 22. Comparison of ACL and PCL Injuries

	Anterior Cruciate Ligament	Posterior Cruciate Ligament
Anatomy	Originates from medial wall of lateral femoral condyle, inserts at the anteromedial and posterolateral intercondyloid eminence of the tibial plateau	Originates at the lateral wall of medial femoral condyle, inserts at the posterior intercondyloid eminence of the tibial plateau
Mechanism	Non-contact (more common): sudden deceleration with change of direction or landing maneuver (anterior tibial translation with valgus knee stress) Contact: direct blow to lateral aspect of knee	Non-contact (less common): hyperflexion or hyperextension Contact: sudden posterior displacement of tibia when knee is flexed or hyperextended (e.g. dashboard MVC injury)
History	Audible "pop" Immediate swelling Knee "giving way" Inability to continue activity	Audible "pop" Immediate swelling Pain with push off Cannot descend stairs
Physical	Effusion (hemarthrosis) Posterolateral joint line tenderness Positive anterior drawer Positive Lachmann Pivot shift Test for collateral ligament and meniscal injuries Look for fracture on x-ray	Effusion (hemarthrosis) Anteromedial joint line tenderness Positive posterior drawer Reverse pivot shift Other ligamentous, bony injuries
Treatment	Stable knee with minimal functional impairment: immobilization 2-4 wk with early ROM and strengthening High demand lifestyle: ligament reconstruction	Unstable knee or young person/high-demand lifestyle: ligament reconstruction

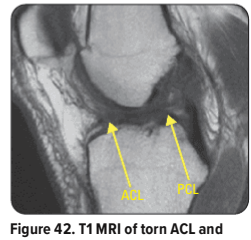


Figure 42. T1 MRI of torn ACL and PCL

Collateral Ligament Tears

Mechanism
- valgus force to knee = MCL tear
- varus force to knee = LCL tear

Clinical Features
- swelling/effusion
- tenderness above and below joint line medially (MCL) or laterally (LCL)
- joint laxity with varus (LCL) or valgus (MCL) stress tests
  - laxity with endpoint suggests partial tear
  - laxity with no endpoint suggests a complete tear
- test for other injuries (e.g. O'Donoghue's unhappy triad), common peroneal nerve injury

Investigations
- x-ray: AP and lateral views of the knee; MRI

Treatment
- non-operative
  - partial tear: immobilization x 2-4 wk with early ROM and strengthening
  - complete tear: immobilization at 30° flexion
- operative
  - indication: multiple ligamentous injuries
  - surgical repair of ligaments

O'Donoghue's Unhappy Triad
- ACL rupture
- MCL rupture
- Meniscal damage (medial and/or lateral)

Meniscal Tears

- medial tear much more common than lateral tear

Mechanism
- twisting force on knee when it is partially flexed (e.g. stepping down and turning)
- requires moderate trauma in young person, but only mild trauma in elderly due to degeneration

Clinical Features
- immediate pain, difficulty WB, instability, and clicking
- increased pain with squatting and/or twisting
- effusion (hemarthrosis) with insidious onset (24-48 h after injury)
- joint line tenderness medially or laterally
- locking of knee (if portion of meniscus mechanically obstructing extension)

Investigations
- MRI, arthroscopy

Treatment
- non-operative
  - indication: not locked, degenerative tear in the presence of osteoarthritis
  - ROM and strengthening (NSAIDs)
- operative
  - indication: locked knee is a surgical emergency (i.e. patient cannot fully extend knee, due to mechanical block) or failed non-operative treatment
  - arthroscopic repair/partial meniscectomy generally indicated for younger patients with traumatic/non-degenerative meniscus pathology

Meniscal repair may be performed in select patients if tear is peripheral with good vascular supply, is a longitudinal tear, and 1-4 cm in length
Partial meniscectomy may be performed when tears are not amenable to repair (complex, degenerative, radial)

Tissue Sources for ACL Reconstruction
- Hamstring autograft
- Middle 1/3 patellar tendon (bone-patellar-bone autograft)
- Allograft (e.g. cadaver)

Popliteal Cysts

- synovial fluid-filled mass located in the popliteal fossa (i.e. Baker's cyst)

Etiology
- classified as primary (distension of the bursa with no communication to joint) or secondary (communication between bursa and joint, bursa fills with articular fluid)
- primary cysts are usually congenital in children, while secondary cysts are acquired from degenerative/inflammatory joint disease in adults

Clinical Features
- usually asymptomatic bulge on the posterior aspect of the knee
- usually located between the semimembranosus and medial head of gastrocnemius
- may cause local tightness, restricted range of motion, or posterior knee pain
- symptoms may worsen with physical activity
- for secondary popliteal cysts, symptoms are more associated with the underlying condition of the knee

Investigations
- clinical diagnosis is often sufficient
- ultrasonography can be used to identify cyst and its relation to adjacent soft tissue structures
- knee x-ray to assess for joint abnormalities that may be associated with the cyst
- MRI allows for clearest visualization but this is only indicated to plan for surgery, when an underlying knee pathology such as a meniscal tear is suspected, or when the diagnosis is uncertain after ultrasonography

Treatment
- asymptomatic cysts do not require treatment
- non-operative
  - indication: initial treatment for symptomatic secondary popliteal cysts
  - identify and treat underlying cause
  - rest, NSAIDs, cold packs for symptomatic treatment
  - image guided aspiration and intra-articular steroid injection may offer temporary relief

Quadriceps/Patellar Tendon Rupture

Mechanism
- sudden forceful contraction of quadriceps during an attempt to decelerate
- eccentric loading of the extensor mechanism, usually with the foot planted and the knee slightly bent
  - DM, SLE, RA, steroid use, renal failure on dialysis
- more common in obese patients with pre-existing degenerative changes in tendon

Clinical Features
- inability to extend knee or weight-bear
- tenderness and/or palpable gap at rupture site
- possible audible "pop"
- patella in lower or higher position with palpable gap above or below patella, respectively
- may have an effusion

Patella alta = high riding patella
Patella baja = low riding patella

Investigations
- ask patient to perform straight leg raise (unable to with complete rupture, although may be inhibited by pain, if unclear, can reassess in 10 d)
- knee x-ray to rule out patellar fracture, MRI to distinguish between complete and partial tears
- lateral view: patella alta with patellar tendon rupture, patella baja with quadriceps tendon rupture

Treatment
- non-operative
  - indication: incomplete tears with preserved extension of knee
  - immobilization in brace, followed by progressive physiotherapy
- operative
  - indication: complete ruptures with loss of extensor mechanism function
- early surgical repair: better outcomes compared with delayed repair (>6 wk post-injury)
- delayed repair complicated by quadriceps contracture, patella migration, and adhesions

Dislocated Knee

Mechanism
- high energy trauma more common (i.e. MVC), low energy (sport-related), or ultra-low velocity (obesity)
- by definition, caused by tears of multiple ligaments

Schenck Classification
Type 1
Singe cruciate (ACL or PCL) and single collateral (MCL or PLC)
Type 2
Injury to ACL and PCL
Type 3-M
Injury to ACL, PCL, and MCL
Type 3-L
Injury to ACL, PCL, and PLC
Type 4
Injury to ACL, PCL, MCL, LCL
Type 5
Multiligamentous injury associated with fracture/dislocation of knee

Clinical Features
- knee instability
- effusion
- pain
- ischemic limb, neurological deficit, or compartment syndrome

Classification
- Kennedy classification (based on direction of tibial displacement) classified by relation of tibia with respect to femur
  - anterior, posterior, lateral, medial, rotary
- Schenck classification (based on pattern of ligamentous injury)

Investigations
- x-ray: AP and lateral
  - associated radiographic findings may include extensor mechanism injury, tibial plateau fracture dislocations, proximal fibular fractures, and/or avulsion of fibular head
- assessment of NVS:
  - ABI (abnormal if <0.9)
  - arteriogram or CT angiogram if abnormal vascular exam (such as abnormal pedal pulses or abnormal ABI)
  - detailed neurologic assessment, paying close attention to the peroneal nerve (foot drop is common)

Treatment
- urgent closed reduction and immobilization
  - can be complicated by interposed soft tissue (posterolateral variant)
- assessment and management of neurovascular injuries and compartment syndrome
- emergent operative repair if vascular injury, open injury, irreducible or grossly unstable dislocation, or compartment syndrome
- ligament reconstruction to restore knee stability is typically performed in a delayed fashion
- early, comprehensive physiotherapy

Specific Complications
- high incidence of associated injuries (tibia/fibula fracture, extensor mechanism injury)
- popliteal artery injury
- peroneal nerve injury
- chronic: instability, stiffness, post-traumatic arthritis

Patella

Patellar Fracture

Mechanism
- direct impact injury: fall, MVC (e.g. dashboard)
- indirect trauma: rapid knee flexion against contracted quadriceps (rare)

Clinical Features
- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- ± effusion/hemarthrosis

Investigations
- x-rays: AP, lateral, skyline
- do not confuse with bipartite patella: congenitally unfused ossification centers with smooth margins on x-ray at superolateral corner (most often)

Treatment
- non-operative
  - indication: non or minimally displaced (step-off <2-3 mm and fracture gap <1-4 mm) or intact extensor mechanism
  - straight leg immobilization 1-4 wk with removable brace/splint, WB as tolerated
  - progress in flexion after 2-3 wk
  - physiotherapy: quadriceps strengthening when pain has subsided
- straight leg immobilization 1-4 wk with removable brace/splint, WB as tolerated
- progress in flexion after 2-3 wk
- physiotherapy: quadriceps strengthening when pain has subsided
- operative
  - indication: >2 mm articular step-off, >3 mm fragment separation, comminuted, disrupted extensor mechanism, open fracture
  - ORIF, if comminuted may require partial/complete patellectomy
    - goal: restore extensor mechanism with maximal articular congruency

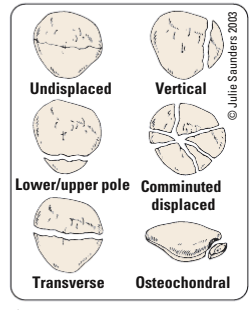


Figure 43. Types of patellar fractures

Complications
- Symptomatic hardware
- Loss of reduction
- Osteonecrosis
- Hardware failure
- Knee stiffness
- Nonunion
- Infection
- Post-traumatic arthritis

Patellar Dislocation

Mechanism
- usually a non-contact twisting injury with knee extended, externally rotated tibia and fixed foot
- lateral displacement of patella after contraction of quadriceps at the start of knee flexion in an almost straight knee joint
- direct blow (e.g. knee/helmet to knee collision)

J-sign: Associated with patella alta; increased lateral translation in extension which pops into the patellofemoral groove as the patella engages the trochlea early in flexion

Risk Factors
- 2nd-3rd decade of life, female
- Q-angle (quadriceps angle) ≥15° (males), ≥20° (females)
  - miserable malalignment syndrome: femoral anteversion, genu valgum, external tibial torsion/ pronated feet
- high-riding patella (patella alta)
- weak vastus medialis
- ligamentous laxity (e.g. Ehlers-Danlos, Marfan Syndrome)

Clinical Features
- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced
- positive patellar apprehension test
  - passive lateral translation results in guarding and patient apprehension
- often recurrent, self-reducing
- concomitant MCL injury
- J-sign

Investigations
- x-rays: AP, lateral, and skyline views of the knee
- check for fracture of medial patella (most common) and lateral femoral condyle
- consider MRI in young patient if concerned for osteochondral injury/loose body

Treatment
- non-operative first
  - closed reduction
  - NSAIDs, activity modification, and physical therapy
  - short-term immobilization for comfort, then 6 wk controlled motion
  - progressive WB and isometric quadriceps strengthening
- operative
  - indication: if recurrent or loose bodies present
  - chronic instability: surgical tightening of medial capsule and release of lateral retinaculum, possible medial patellofemoral ligament (MPFL) reconstruction
  - patellar dislocation associated with congenital deformity: tibial tuberosity transfer

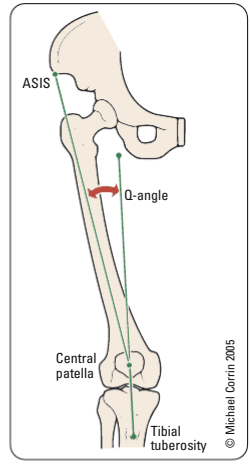


Figure 44. Q-angle
The angle between a vertical line through the patella and tibial tuberosity and a line from the ASIS to the middle patella; the larger the angle, the greater the amount of lateral force on the knee (normal <20°)

Patellofemoral Syndrome

- syndrome of anterior knee pain associated with idiopathic articular changes of patella

Risk Factors
- malalignment causing patellar maltracking (Q-angle ≥20°, genu valgus)
- female > male, physically active, <40 y/o
- excessive knee strain (athletes, especially running and weight training)
- recurrent patellar dislocation, ligamentous laxity, post-trauma
- deformity of patella or femoral groove

Mechanism
- softening, erosion, and fragmentation of articular cartilage, predominantly medial aspect of patella

Clinical Features
- diffuse pain in peri- or retropatellar area of knee (major symptom)
  - exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting, or kneeling
- insidious onset and vague in nature
- sensation of instability, pseudolocking
- pain with compression of patella with knee ROM or with resisted knee extension
- swelling rare, minimal if present
- palpable crepitus

Pain with firm compression of patella into medial femoral groove is pathognomonic of patellofemoral syndrome

Investigations
- x-ray: AP, lateral, and skyline views of the knee – may find chondrosis, lateral patellar tilt, patella alta/ baja, or shallow sulcus
- CT: patellofemoral alignment, rule out fracture
- MRI: best to assess articular cartilage

Treatment
- non-operative
  - continue non-impact activities; rest and rehabilitation
  - NSAIDs
  - physiotherapy: vastus medialis, core, and hip strengthening
- operative
  - indication: failed non-operative treatment
  - arthroscopic debridement
  - lateral release of retinaculum
  - patellar realignment (e.g. anterior tubercle elevation)

Tibia

Tibial Plateau Fracture

Mechanism
- varus/valgus load ± axial loading (e.g. fall from height)
- femoral condyles driven into proximal tibia
- can result from minor trauma in those with osteoporosis

Clinical Features
- frequency: lateral > bicondylar > medial
- medial fractures require higher energy – often have concomitant vascular injuries
- knee effusion, swelling
- may have severe soft tissue injury that requires delay in ORIF for 1-2 wk
- inability to bear weight
- risk of compartment syndrome, meniscal tears, and neurovascular injuries
- Schatzker classification

Schatzker Classification

Type	Description
I	Lateral plateau split fracture
II	Lateral split-depressed fracture
III	Lateral pure depression fracture
IV	Medial plateau fracture
V	Bicondylar plateau fracture
VI	Bicondylar with metaphyseal/diaphyseal disassociation

Investigations
- x-ray: AP, lateral, and oblique views
- CT: preoperative planning, identify articular depression and comminution
- ABI if any differences in pulses between extremities

Treatment
- non-operative
  - indication: # depression is <3 mm
  - protected WB with immobilization in a splint for 6-12 wk with early progressive ROM
- operative
  - indication: articular step-off >3 mm, condylar widening >5 mm, open #s, neurovascular injury, significant varus/valgus instability (>15°)
  - ORIF often requiring bone grafting to elevate depressed fragment

Specific Complications (see *General Fracture Complications, OR7*)
- post-traumatic OA
- meniscal lesions

Tibial Shaft Fracture

- most common long bone fracture and open fracture

Mechanism
- low energy pattern: torsional injury
- high energy: including MVC, falls, sporting injuries

Clinical Features
- pain, inability to weight-bear, deformity
- open vs. closed
- neurovascular compromise
- compartment syndrome
- may have severe soft tissue injury that requires delay in ORIF for 1-2 wk

Investigations
- x-ray: full length AP and lateral views
  - AP, lateral, and oblique views of ipsilateral knee and ankle
  - consider dedicated ankle x-rays or CT scan to rule out intra-articular extension of middle third or distal tibia shaft fractures

Figure 45. Tibial shaft fracture treated with IM nail and screws

Tibial shaft fractures have high incidence of compartment syndrome and are often associated with soft tissue injuries

Treatment
- non-operative
  - indication: closed and minimally displaced or adequate closed reduction
  - long leg cast x 6-8 wk, convert to functional (patellar tendon bearing) brace for another 6 wk with progressive WB
- operative
  - indication: displaced or open
  - if displaced and closed: ORIF with IM nail, plate and screws, or external fixator
  - if open: antibiotics, I&D, external fixation or IM nail, and vascularized coverage of massive soft tissue defects

Specific Complications (see General Fracture Complications, OR7)
- significant incidence of compartment syndrome
- knee pain associated with infrapatellar IM nailing (>50% anterior knee pain)
- malunion, nonunion
- lack of soft tissue coverage secondary to open fracture may require further surgery for muscle flap coverage

Ankle

Evaluation of Ankle and Foot Complaints

Special Tests
- anterior drawer: examiner stabilizes the tibia with one hand and attempts to displace the foot anteriorly with the contralateral hand with the ankle held in neutral or plantar flexion
- talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated

X-Ray
- AP, mortise, and lateral views
- mortise view: ankle at 15° of internal rotation
  - gives true view of ankle joint
  - joint space should be symmetric with no talar tilt
- Ottawa Ankle and Foot Rules should guide x-ray use (see Emergency Medicine, ER16); nearly 100% sensitivity
- ± CT to better characterize fractures

Ankle Fracture

Mechanism
- pattern of fracture depends on the position of the foot when trauma occurs
- classification systems
  - Danis-Weber: based on location of main fibular fracture line relative to the syndesmosis
  - Lauge-Hansen: based on foot position and direction of applied stress/force

Treatment
- non-operative
  - indication: non-displaced, Danis-Weber Type A, and some isolated undisplaced Danis-Weber Type B
  - early protected WB in walking boot
- operative
  - indications
    - fracture-dislocation
    - most Danis-Weber Type B, and all Type C
    - any talar displacement
    - displaced isolated medial or lateral malleolar fracture
    - trimalleolar (medial, posterior, lateral) fractures
    - displaced and large posterior malleolar fractures
    - persistent medial clear space widening despite attempt at closed reduction and immobilization
    - open fracture/open joint injury
  - ORIF with plates and screws

Complications
- risk of poor wound healing and deep infections (up to 20%) in patients with DM, particularly if concomitant peripheral neuropathy
- postoperative stiffness
- malunion, nonunion
- post-traumatic arthritis

Danis-Weber Classification
- Based on level of fibular fracture relative to syndesmosis
- Type A (infra-syndesmotic)
- Pure inversion injury, tibiofibular syndesmosis remains intact
- Avulsion of lateral malleolus below plafond or torn calcaneofibular ligament
- ± shear fracture of medial malleolus
- Type B (trans-syndesmotic)
- External rotation and eversion (most common)
- ± avulsion of medial malleolus or rupture of deltoid ligament
- Spiral fracture of lateral malleolus starting at plafond
- Type C (supra-syndesmotic)
- Pure external rotation
- Avulsion of medial malleolus or torn deltoid ligament
- ± posterior malleolus avulsion with posterior tibio-fibular ligament
- Fibular fracture is above plafond
- Frequently tears syndesmosis

Ottawa Ankle and Foot Rules
(see Emergency Medicine, ER16)
X-rays are only required if:
Pain in the malleolar zone AND any of: bony tenderness over posterior or tip of lateral malleolus; OR bony tenderness over posterior or tip of medial malleolus; OR inability to weight bear both immediately after injury and in the ER

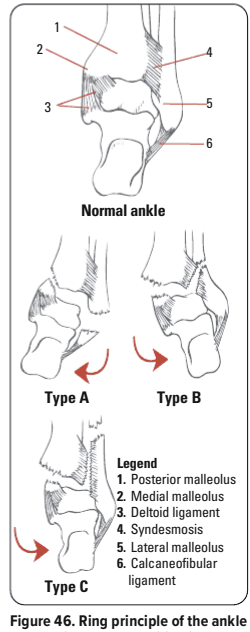


Figure 46. Ring principle of the ankle and Danis-Weber classification

Ankle Ligamentous Injuries

Medial Ligament Complex (deltoid ligament)
(deltoid ligament: comprised of anterior tibiotalar, tibiocalcaneal, posterior tibiotalar, tibionavicular)
- eversion injury
- usually avulses medial or posterior malleolus and strains syndesmosis

Lateral Ligament Complex
(anterior talofibular, calcaneofibular, posterior talofibular)
- inversion injury, >90% of all ankle sprains
- anterior talofibular (ATFL) most commonly and severely injured if ankle is plantarflexed
- swelling and tenderness anterior to lateral malleolus
- ++ ecchymosis
- positive ankle anterior drawer
- may have significant medial talar tilt on inversion stress x-ray

Treatment
- non-operative
  - microscopic tear (Grade I)
    - rest, ice, compression, elevation
  - macroscopic tear (Grade II)
    - strap ankle/aircast for up to a few weeks, should not interfere with early rehabilitation; NSAIDs
    - physiotherapy: strengthening and proprioceptive retraining
  - complete tear (Grade III)
    - below knee walking boot x 4-6 wk (controversial and variable); NSAIDs
    - physiotherapy: strengthening and proprioceptive retraining
    - surgery: may be required if chronic symptomatic instability develops

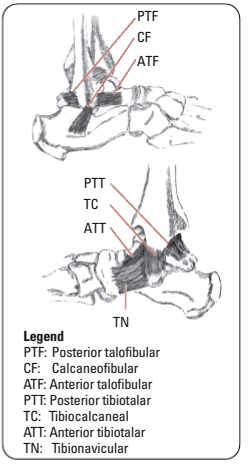


Figure 47. Ankle ligament complexes

With a history of significant trauma from axial loading of lower limb, always consider spinal injuries and talar/calcaneal fractures

Foot

Talar Fracture

Mechanism
- forced dorsiflexion with axial load, commonly from MVC or fall from height
- 60% of talus covered by articular cartilage; fractures often intra-articular
- talar neck is most common fracture of talus (50%)
- non-neck talus fractures are rare, and can include talar body (15-25%), process (10%), or head fractures
- tenuous blood supply runs distal to proximal along talar neck
  - high-risk of AVN with displaced fractures

Investigations
- x-ray: AP, lateral, and Canale views (maximum equinus, 15° pronated) of the foot
- CT characterize fracture and assess for ipsilateral foot injuries (up to 88% incidence)
- MRI: acutely unhelpful; may define extent of AVN during follow-up

Treatment
- non-operative
  - indication: non-displaced
  - emergent reduction in ER, below-knee cast 8-12 wk (NWB first 6 wk)
- operative
  - indication: displaced
  - ORIF

Complications
- AVN (~30% risk of osteonecrosis)
- malunion/nonunion
- post-traumatic arthritis (subtalar most common)

Calcaneal Fracture

- most common tarsal fracture

Mechanism
- high energy axial loading: fall from height onto heels, MVA
- 75% are intra-articular and 10% are bilateral
- 10% of fractures associated with compression fractures of thoracic or lumbar spine (rule out spine injury)

Calcaneal Fracture Treatment Principles
- Avoid wound complications (10-25%)
- Restore articular congruity
- Restore normal calcaneal width and height
- Maximum functional recovery may take longer than 12 mo

Clinical Features
- marked swelling, pain, inability to weight bear, bruising on heel/sole
- wider, shorter, flatter heel when viewed from behind
  - may have apparent varus deformity

Investigations
- x-rays: AP, lateral, and oblique foot (mandatory views); Broden view, Harris view, or AP ankle (optional)
  - loss of Bohler's angle, double-density sign
- CT: gold-standard, assess intra-articular extension

Treatment
- closed vs. open reduction is controversial
- NWB cast x 6-12 wk with early ROM and strengthening

Complications
- wound complications
- subtalar arthritis
- compartment syndrome
- malunion

Haglund Deformity: an enlargement of the posterior-superior tuberosity of the calcaneus

Achilles Tendonitis

- Achilles: largest tendon in the body
- formed by confluence of soleus and gastrocnemius tendons

Mechanism
- chronic inflammation from activity or poor-fitting footwear
- may develop painful heel bumps (i.e. retrocalcaneal bursitis or Haglund deformity)

Clinical Features
- posterior heel pain, swelling, burning, stiffness
- thickened tendon, palpable bump

Investigations
- x-ray: lateral, evaluate bone spur and calcification
- U/S, MRI can assess degenerative change

Treatment
- non-operative
  - rest, NSAIDs, activity and shoe wear modification (orthotics, open back shoes)
  - heel sleeves and pads are mainstay of non-operative treatment
  - gentle gastrocnemius-soleus stretching, eccentric training with physical therapy, deep tissue calf massage
  - shockwave therapy in chronic tendonitis
  - avoid steroid injections (risk of Achilles tendon rupture)
- operative
  - open or arthroscopic debridement of Haglund lesion

The most common site of Achilles tendon rupture is 2-6 cm from its insertion where the blood supply is the poorest

Achilles Tendon Rupture

Mechanism
- sudden forced plantar flexion, violent dorsiflexion when plantar flexed
- loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
- secondary to chronic tendonitis, steroid injection, fluoroquinolone antibiotics

Clinical Features
- audible "pop," sudden pain with push-off movement
- pain or weakness/inability to plantarflex
- palpable gap
- apprehensive toe off when walking
- Thompson test: with patient prone, squeeze calf, normal response is plantar flexion
  - no passive plantarflexion is positive test = ruptured tendon

Investigations
- x-ray: rule out other pathology
- U/S or MRI: differentiate between partial vs. complete ruptures

Complications of Achilles Tendon Rupture

Infection/wound healing complications (operative management)

Sural nerve injury (operative management)

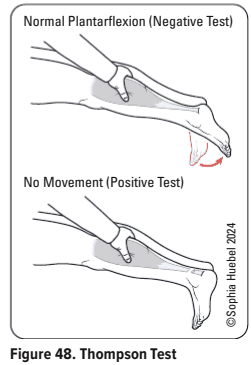


Figure 48. Thompson Test

Treatment
- non-operative
  - indication: low functional demand (level 1 evidence suggests no difference in re-rupture rates between operative and non-operative management with functional rehabilitation)
  - functional bracing/casting in resting equinus (plantar flexion), with functional rehabilitation x 12 wk
- operative
  - indication: high functional demand (e.g. professional athlete)
  - surgical repair, followed by functional rehabilitation x 12 wk

Plantar Fasciitis

Definition
- inflammation of plantar aponeurosis at calcaneal origin
- common in athletes (especially runners, dancers)
- also associated with obesity, DM, inflammatory arthropathies

Mechanism
- repetitive strain injury causing microtears and inflammation of plantar fascia

Clinical Features
- insidious onset of heel pain, often when getting out of bed, and stiffness
- intense pain when walking from rest that subsides with ambulation; worse at end of day after prolonged standing
- tenderness to palpation at medial tuberosity of calcaneus
- pain with toe dorsiflexion (stretches fascia) and palpation of fascia from heel to forefoot

Investigations
- x-ray to rule out fractures, may show plantar heel spur
- spur is secondary to inflammation, not the cause of pain

Treatment
- non-operative
  - pain control and stretching programs are first-line
  - rest, ice, NSAIDs, steroid injection
  - physiotherapy: Achilles tendon and plantar fascia stretching, extracorporeal shockwave therapy
  - orthotics with heel cup – to counteract pronation and disperse heel strike forces
- operative
  - very rarely indicated
  - when performed, includes endoscopic release of fascia

Bunions (Hallux Valgus)

Definition
- bony deformity characterized by medial displacement of first metatarsal and lateral deviation of hallux

Mechanism
- valgus alignment of 1st MTP (hallux valgus), loose medial and tight lateral joint capsule, adductor hallucis becomes a deforming force
- formation of a reactive exostosis and thickening of the skin creates a bunion
- associated with poor-fitting footwear (high heel and narrow toe box)
- can be hereditary (70% have family history)
- more frequent in women

Clinical Features
- painful bursa over medial eminence of 1st MT head
- pronation (rotation inward) of great toe
- numbness over medial aspect of great toe

Investigations
- x-ray: standing AP, lateral, and oblique views; sesamoid can be helpful

Treatment
- indications: painful corn or bunion, overriding 2nd toe
- non-operative (first-line)
  - properly fitted shoes (low heel) and toe spacer
- operative: persistent symptoms, goal is to restore normal anatomy, not cosmetic reasons alone
  - osteotomy with realignment of 1st MTP joint
  - arthrodesis

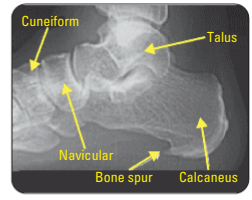


Figure 49. X-ray of bony heel spur

Surgical vs. Nonsurgical Methods for Acute Achilles Tendon Rupture: A Meta-Analysis of Randomized Controlled Trials
J Foot Ankle Surg Am 2018 Nov - Dec; 57(6): 1191-1199
Purpose: To compare surgical treatment and conservative treatment of acute Achilles tendon rupture.
Methods: A meta-analysis was performed looking at randomized trials comparing surgical with nonsurgical treatment or comparing different surgical treatments of Achilles tendon rupture.
Results: 10 randomized clinical trials with a total of 934 randomized patients were included. Patients in the non-surgical group had a higher re-rupture rate than patients in the surgical group. However, re-rupture rates were equivalent (P = .08) if an early range of motion exercises protocol was performed. Lower incidence of complications (excluding re-rupture) was found in non-surgical patients.
Conclusions: Non-surgical treatment for acute Achilles tendon rupture is preferred if a functional rehabilitation protocol with early range of motion is possible. If not, surgical treatment should be considered because of the lower rate of re-rupture.

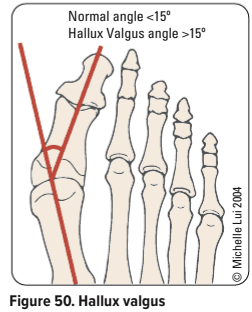


Figure 50. Hallux valgus

Metatarsal Fracture

- use Ottawa Foot Rules to determine need for x-ray

Table 23. Types of Metatarsal Fractures

Fracture Type	Mechanism	Clinical Features	Treatment
Avulsion of Base of 5th MT	Sudden inversion followed by contraction of peroneus brevis	Tender base of 5th MT	Conservative management
Proximal Shaft of 5th MT (Jones Fracture)	Stress injury	Painful over base of 5th MT	*NWB BK cast x 6-8 wk
Shaft 2nd, 3rd MT (March Fracture)	ORIF if athlete, displacement, or skin tenting	Painful shaft of 2nd or 3rd MT	Symptomatic (protected weight bearing, pain management)
1st MT	Trauma	Painful 1st MT	ORIF if displaced otherwise *NWB BK cast x 3 wk then walking cast x 2 wk
Tarso-MT Fracture – Dislocation (Lisfranc Fracture)	Forceful axial load on a plantar flexed foot or direct crush injury	Pain over base of 2nd MT Swelling over midfoot Inability to bear weight Bruising on plantar aspect of midfoot	ORIF or arthrodesis if displaced Cast immobilization if undisplaced x 8-12 wk

*NWB BK = Non weight bearing, below knee

Ottawa Ankle and Foot Rules
(see Emergency Medicine, ER16)
X-rays only required if:
Pain in the midfoot zone AND any of:
bony tenderness over the navicular or base of the fifth metatarsal; OR inability to weight bear both immediately after injury and in the ER

Pediatric Orthopedics

Fractures in Children

- type of fracture
  - thicker, more active periosteum results in pediatric-specific fractures: greenstick (one cortex), torus (i.e. 'buckle', impacted cortex) and plastic (bowing)
  - distal radius fracture most common in children (phalanges second), the majority are treated with closed reduction and casting
- epiphyseal growth plate
  - weaker part of bone, susceptible to injuries
  - growth plate often mistaken for fracture on x-ray and vice versa (x-ray opposite limb for comparison), especially in elbow
  - tensile strength of bone < ligaments in children, therefore clinician must be confident that fracture and/or growth plate injury have been ruled out before diagnosing a sprain
  - intra-articular fractures have worse consequences in children because they usually involve the growth plate, and may affect future bone growth
- anatomic reduction
  - gold standard with adults
  - may accept greater angular deformity in children as remodeling minimizes deformity at skeletal maturity
- time to heal
  - shorter in children
- always be aware of the possibility of child abuse (non-accidental injury, NAI)
  - ensure stated mechanism is compatible with injury presentation
  - high index of suspicion with fractures in non-ambulating children (<1 yr); look for other signs, including x-ray evidence of healing fractures at different sites and different stages of healing
  - common suspicious fractures in children: metaphyseal corner fracture (hallmark of non-accidental trauma), femur fracture <1 y/o, humeral shaft <3 y/o, sternal fractures, posterior rib fractures, spinous process fractures
  - if concerned for NAI, admit child to hospital, contact appropriate authorities, engage allied health such as social work, and treat injuries as normal

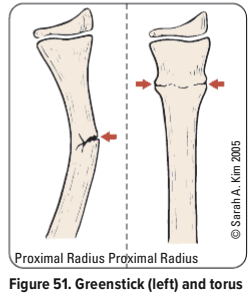


Figure 51. Greenstick (left) and torus (right) fractures

Greenstick fractures are easy to reduce but can redisplace while in cast due to intact periosteum

Stress Fractures

Mechanism

- insufficiency fracture
  - normal or physiologic stress applied to a weak or structurally deficient bone
- fatigue fracture
  - repetitive, excessive force applied to normal bone
- most common in adolescent athletes
- common in tibia, calcaneus, and metatarsals

Diagnosis
- localized pain and tenderness over the involved bone
- plain films may not show fracture initially
- bone scan positive in 12-15 d, MRI demonstrates abnormal edema

Treatment
- rest from strenuous activities to allow remodeling (can take several months)
- protected weight bearing
- splinting/Aircast optional

Physeal Injury

Table 24. Salter-Harris Classification of Epiphyseal Injury

SALT(E)R–Harris Type	Description	Treatment
I (Straight through; Stable)	Transverse through growth plate	Closed reduction and cast immobilization; heals well, 95% do not affect growth
II (Above)	Through metaphysis and along growth plate	Closed reduction and cast if anatomic; otherwise closed ± open reduction, internal fixation
III (Below)*	Through epiphysis to plate and along growth plate	Anatomic reduction by ORIF to prevent growth arrest, avoid fixation across growth plate
IV (Through and through)*	Through epiphysis and metaphysis	Closed reduction and cast if anatomic; otherwise ORIF
V (Ram)*	Crush injury of growth plate	Cast immobilization (operative management is rarely indicated): high incidence of growth arrest

* Types III – V are more likely to cause growth arrest and progressive deformity

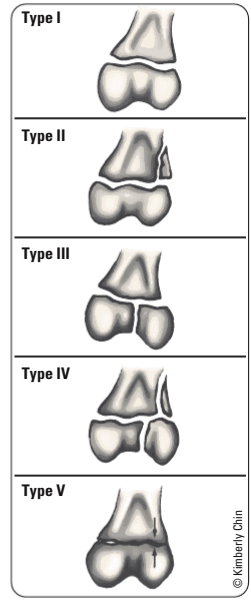


Figure 52. Salter-Harris classification of epiphyseal injury

Slipped Capital Femoral Epiphysis

- most common adolescent hip disorder, peak incidence at pubertal growth spurt

Definition
- type I Salter-Harris epiphyseal injury at proximal hip with anterosuperior displacement of the metaphysis relative to the epiphysis (remains in the acetabulum)

Etiology
- multifactorial
  - genetic: autosomal dominant, Black children at highest risk
  - cartilaginous physis hypertrophies too rapidly under growth hormone effects
  - overweight: mechanical stress
  - trauma: causes acute slip
- risk factors: obesity (No.1 factor), male, hypothyroid, growth hormone deficiency, previous radiation to hip region, renal osteodystrophy, Down Syndrome

Clinical Features
- acute: sudden, severe pain with limp, less than 3 wk duration
- chronic: typically groin and anterior thigh pain, may present with knee
  - positive Trendelenburg sign on affected side, due to weakened gluteal muscles
- can be associated with knee pain due to activation of the medial obturator nerve
- restricted internal rotation, abduction, flexion
  - Drehmann sign: obligatory external rotation during passive flexion of hip
- Loder classification: stable vs. unstable (provides prognostic information)
  - stable = able to bear weight, with or without crutches (risk of osteonecrosis <10%)
  - unstable = unable to ambulate even with crutches (high-risk of osteonecrosis, between 24-47%)

Bilateral involvement occurs in about 25%

Klein's Line
On AP view, line drawn along superolateral border of femoral neck should cross at least a portion of the femoral epiphysis. If it does not, suspect SCFE

Investigations
- x-ray: AP, frog-leg lateral radiographs both hips
  - posterior and medial slip of epiphysis
  - disruption of Klein's line
  - AP view may be normal or show widened/lucent growth plate compared with opposite

Treatment
- operative: percutaneous in-situ fixation without reduction (reduction is highly controversial)
- consider prophylactic fixation of contralateral hip in high-risk patients

Complications
- AVN, chondrolysis (loss of articular cartilage, resulting in narrowing of joint space), pin penetration, premature OA, loss of ROM, contralateral SCFE

Developmental Dysplasia of the Hip

Definition

- abnormal development of hip, resulting in shallow acetabulum (dysplasia), displacement with some remaining contact between the articular surfaces (subluxation), or complete displacement of the joint (dislocation)
- most common orthopedic disorder in newborns
- all newborns require screening with physical exam

Etiology

- due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
- spectrum of conditions
  - dysplastic acetabulum, more shallow, and more vertical than normal
  - head subluxates out of joint when provoked
  - dislocatable head in socket
  - dislocated femoral head completely out of acetabulum

Physical Exam

- diagnosis is clinical
  - limited abduction of the flexed hip (<60°)
  - affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
  - Barlow's test demonstrates whether hips are dislocatable
    - flex hips and knees to 90° and grasp thigh
    - fully adduct hips, push posteriorly to try to dislocate hips, feeling for a distinct clunk
  - Ortolani's test demonstrates whether hips are reducible
    - initial position as above but try to reduce hip with fingertips during abduction
    - positive test: palpable clunk is felt (not heard) if hip is reduced
  - Trendelenburg test and gait useful if older (>2 yr)
  - Galeazzi's sign
    - knees at unequal heights when hips and knees flexed
    - appearance of a shorter femur (lower knee) on affected side
    - difficult test if child <1 yr

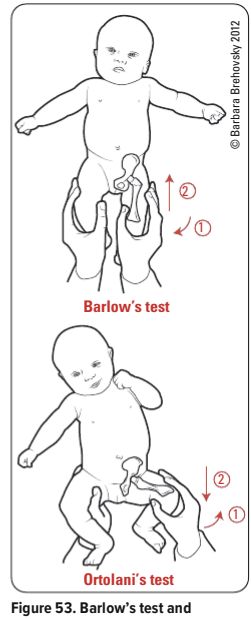


Figure 53. Barlow's test and Ortolani's test

Investigations

- perform screening U/S at 4-6 weeks in patients with risk factors and positive physical findings to view cartilage (bone is not calcified in newborns until 4-6 mo)
- follow-up radiograph after 3 mo
- x-ray signs (at 4-6 mo): false acetabulum, acetabular index >25°, broken Shenton's line, femoral neck above Hilgenreiner's line (horizontal line through right and left triradiate cartilage), ossification centre outside of inner lower quadrant (quadrants formed by intersection of Hilgenreiner's and Perkin's lines)

5 Fs that Predispose to Developmental Dysplasia of the Hip
Family history
Female
Frank breech
First born
Le**F**t hip

Treatment

- 0-6 mo: reduce hip using Pavlik harness to maintain abduction and flexion
- 6-18 mo: reduction under GA, hip spica cast x 2-3 mo (if Pavlik harness fails)
- 18 mo-2 yr: open reduction with spica casting
- >2 yr: pelvic and/or femoral osteotomy

Complications

- redislocation, inadequate reduction, stiffness
- AVN of femoral head may be seen at any point in treatment; due to impingement of medial circumflex femoral artery with severe abduction and flexion secondary to prolonged Pavlik harness or spica cast treatment

Legg-Calvé-Perthes Disease (Coxa Plana)

Definition

- idiopathic AVN of femoral head, presents at 4-8 yr of age
- 12% bilateral, M:F=5:1, 1/1200 children
- associations
  - family history of Legg-Calve-Perthes Disease
  - low birth weight
  - abnormal pregnancy/delivery
  - ADHD in 33% of cases, delayed bone age in 89%
  - second-hand smoke exposure
- key features
  - AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodeling of regenerated bone

Most common in adolescent athletes, especially jumping/sprinting sports

Children diagnosed with coxa plana <6 yr of age have improved prognosis

Clinical Features
- child with antalgic or Trendelenburg gait ± pain
- intermittent knee, hip, groin, or thigh pain
- flexion contracture (stiff hip)
- decreased internal rotation and abduction of hip
- limb length discrepancy (late)

Investigations
- x-ray: AP pelvis, frog leg lateral
- initially, may be negative; if high index of suspicion, obtain bone scan or MRI
- eventually, collapse of femoral head will be seen (diagnostic)

Treatment
- goal is to keep femoral head contained in acetabulum and maintain ROM (contain and maintain)
- non-operative
  - physiotherapy: ROM exercises
  - restricted weight bearing
- operative
  - femoral or pelvic osteotomy (>8 yr of age or severe)
    - prognosis better in males, <6 yr, <50% of femoral head involved, abduction >30°
- 60% of involved hips do not require operative intervention
- natural history is early onset OA and decreased ROM

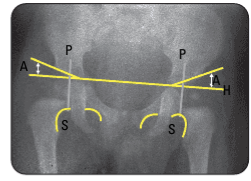


Figure 54. Pelvic x-ray and reference lines and angles for assessment of DDH

Triradiate Cartilage
y-shaped epiphyseal plate at junction of ilium, ischium, and pubis

Hilgenreiner's Line
Line running between triradiate cartilages

Perkin's Line
Line through lateral margin of acetabulum, perpendicular to Hilgenreiner's Line

Shenton's Line
Arced line along inferior border of femoral neck and superior margin of obturator foramen

Acetabular Index
Angle between Hilgenreiner's Line and line from triradiate cartilage to point on lateral margin of acetabulum

Osgood-Schlatter Disease

Definition
- inflammation of patellar ligament at insertion point on tibial tuberosity
- M>F; boys 12-15 yr; girls 8-12 yr

Mechanism
- repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)

Clinical Features
- tender lump over tibial tuberosity
- pain on resisted leg extension
- anterior knee pain exacerbated by jumping or kneeling, relieved by rest

Investigations
- x-ray lateral knee: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

Treatment
- benign, self-limited condition, does not resolve until growth halts
- non-operative (majority)
  - avoid aggravating activities such as basketball or cycling
  - NSAIDs, rest, flexibility, isometric strengthening exercises
  - casting if symptoms do not resolve with conservative management
- operative: ossicle excision in refractory cases (patient is skeletally mature with persistent symptoms)

Congenital Talipes Equinovarus (Club Foot)

Definition
- congenital foot deformity
- muscle contractures resulting in CAVE deformity
- bony deformity: talar neck medial and plantar deviated; varus calcaneus and rotated medially around talus; navicular and cuboid medially displaced

Etiology
- intrinsic causes (neurologic, muscular, or connective tissue diseases) vs. extrinsic (intrauterine growth restriction); may be idiopathic, neurogenic, or syndrome-associated
- fixed deformity
- 1-2 in 1000 newborns, 50% bilateral, M>F ~2:1, severity F>M

Physical Exam
- examine for CAVE deformity
- examine hips for associated DDH
- examine knees for deformity
- examine back for dysraphism (unfused vertebral bodies)
- diagnosis is often from physical exam findings alone, radiographs unnecessary

CAVE deformity
Midfoot **C**avu (tight intrinsics, FHL, FDL)
Forefoot **A**dductus (tight tibialis posterior)
Hindfoot **V**arus tight Achilles tendon, tibialis posterior, tibialis anterior)
Hindfoot **E**quinus (Hindfoot Equinus (tight Achilles tendon)

Treatment
- largely non-operative via Ponseti Technique (serial manipulation and casting)
  - correct deformities in CAVE order
    - change strapping/cast q1-2 wk
    - typically requires percutaneous Achilles tendon release after ~ 2 months of casting with another 3 weeks of casting in maximal dorsiflexion
    - surgical release in refractory case (rare)
- delayed until age 3-4 mo
- 3 yr recurrence rate = 5-10%
- mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf muscle atrophy

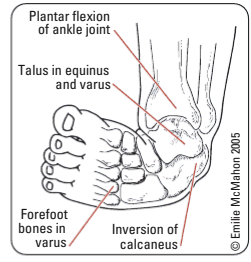

Plantar flexion of ankle joint
Talus in equinus and varus
Forefoot bones in varus
Inversion of calcaneus
© Emilie McMahon 2005

Figure 55. Club foot - depicting the gross and bony deformity

Scoliosis

Definition
- lateral curvature of spine with vertebral rotation
- age: 10-14 yr
- more frequent and more severe in females

Etiology
- idiopathic: most common (90%)
- congenital: vertebrae fail to form or segment
- neuromuscular: UMN or LMN lesion, myopathy
- postural: leg length discrepancy, muscle spasm
- other: osteochondrodystrophies, neoplastic, traumatic

Clinical Features
- cosmetic concern ± back pain
- primary curve where several vertebrae affected
- secondary compensatory curves above and below fixed primary curve to try to maintain normal position of head and pelvis
- asymmetric shoulder height when bent forward
- Adam's test: thoracic or lumbar prominence on affected side with forward bend at the waist
- prominent scapulae, creased flank, asymmetric pelvis
- associated posterior midline skin lesions in neuromuscular scoliosis
  - café-au-lait spots, dimples, neurofibromas
  - axillary freckling, hemangiomas, hair patches
- associated pes cavus or leg atrophy
- apparent leg length discrepancy
- Scoliosis Lenke Classification: guide to select curves to be included within the fusion construct

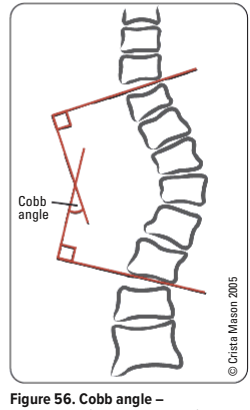


Figure 56. Cobb angle – used to monitor the progression of the scoliotic curve

Investigations
- x-ray: 3-foot standing, AP, lateral
  - measure curvature: Cobb angle
  - may have associated kyphosis

Treatment
- based on Cobb angle
  - <25°: observe for changes with serial radiographs
  - >25° or progressive: bracing (many types, controversial) that halt/slow curve progression but do not reverse deformity
  - >45°, cosmetically unacceptable, or respiratory problems: surgical correction (spinal fusion)

Scoliosis screening is not recommended in Canada (Grieg A, et al. 2010; Health Canada, 1994)

In structural or fixed scoliosis, bending forwards makes the curve more obvious

Postural scoliosis can be corrected by correcting the underlying etiology

Bone Tumours

- primary bone tumours are rare after 3rd decade
- metastases to bone are relatively common after 3rd decade

Clinical Features
- malignant (primary or metastasic): local pain and swelling (weeks to months), worse on exertion and at night, ± soft tissue mass
- minor trauma can be the initiating event that calls attention to lesion

Red Flags
- Persistent skeletal pain
- Localized tenderness
- Spontaneous fracture
- Enlarging mass/soft tissue swelling

Table 25. Distinguishing Benign from Malignant Bone Lesions on X-Ray

Benign	Malignant
No periosteal reaction or benign appearing reaction (e.g. uniform smooth periosteal thickening as seen in a healing fracture)	Acute periosteal reaction • Codman's triangle • "Onion skin" • "Sunburst"
Sharp, well-demarcated borders, narrow zone of transition (between lesion and normal bone, suggesting slow-growing lesion)	Poorly defined borders, with a wide zone of transition, or infiltrative (suggesting fast-growing lesion)
Well-developed bone formation	Varied bone formation
Intraosseous and even calcification	Extraosseous and irregular calcification
No soft tissue mass	Soft tissue mass present
No cortical destruction or uniform cortical destruction in some low grade and locally aggressive benign lesions	Aggressive cortical destruction or tumour infiltration without cortical destruction

Adapted from: Buckholtz RW, Heckman JD. Rockwood and Green's Fractures in Adults. Volume 1. Philadelphia: Lippincott Williams & Wilkins, 2001. p558

Describing Bone Tumours on X-rays
1. Location (which bone and whether it is in the diaphysis, metaphysis, or epiphysis)
2. Size
3. Solitary vs. multifocal
4. Morphology: geographic, permeative, or moth-eaten margins
5. Presence of periosteal reaction
6. Presence of bony remodeling
7. Cortical involvement
8. Matrix: osteoid (cumulus cloud), chondroid (punctate or popcorn calcification), or fibrous (ground glass appearance)
9. Presence of soft-tissue mass
10. Associated pathological fracture

Diagnosis
- malignancy is suggested by rapid growth, warmth, tenderness, aggressive features on imaging
- may be associated with constitutional symptoms such as fevers, night sweats, weight loss, or loss of appetite
- staging should include:
  - local
    - full length radiographs of the affected bone
    - ± CT and/or MRI of affected bone
    - biopsy
  - should be referred to specialized centre for biopsy
  - systemic
    - blood work (CBC, electrolytes, liver function assays, inflammatory markers, bone profile, extended electrolytes including calcium)
    - serum electrophoresis for older patients ± Bence Jones protein
    - CT chest/abdo/pelvis
    - Bone scan or bone marrow biopsy depending on preliminary diagnosis

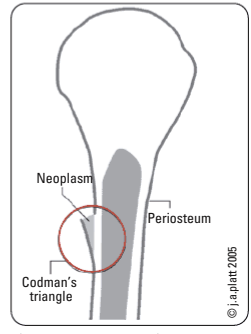


Figure 57. Codman's triangle
A radiographic finding in malignancy, where the partially ossified periosteum is lifted off the cortex by neoplastic tissue

Benign Active Bone Tumours

BONE-FORMING TUMOURS

Osteoid Osteoma
- benign bone tumour arising from osteoblasts; not known to metastasize
- peak incidence in 2nd and 3rd decades, M:F=2-3:1
- proximal femur>tibia diaphysis most common locations; spine (can cause painful scoliosis)
- radiographic findings: small, round radiolucent nidus (<1.5 cm) surrounded by dense sclerotic bone ("bull's-eye")
- symptoms: constant and progressive pain from prostaglandin secretion and COX1/2 expression
  - pain worse at night (diurnal prostaglandin production); characteristically relieved by NSAIDs
- treatment: NSAIDs are first-line; percutaneous radiofrequency ablation or surgical resection for refractory lesions

FIBROUS LESIONS

Fibrous Cortical Defect (i.e. non-ossifying fibroma, fibrous bone lesion)
- developmental defect in which areas that normally ossify are filled with fibrous connective tissue
- most common benign bone tumour in children, typically asymptomatic and an incidental finding
- occur in as many as 35% of children, peak incidence between 2-25 yr old
- distal femur > distal tibia > proximal tibia most common locations
- radiographic findings: diagnostic, metaphyseal eccentric 'bubbly' lytic lesion near physis; thin, smooth/lobulated, well-defined sclerotic margin
  - multiple lesions can be present; large lesions may be associated with pathologic fractures
- treatment: most lesions resolve spontaneously; curettage and bone grafting for symptomatic lesions or to prevent pathologic fractures in larger lesions

Osteochondroma
- cartilage capped bony lesion arising on the external surface of a bone
- 2nd and 3rd decades, M>F
- most common benign bone tumour (~30%); true incidence unknown as many asymptomatic
- 2 types: sessile (broad based and increased risk of malignant degeneration) vs. pedunculated (narrow stalk)
- metaphysis of long bone near tendon attachment sites (distal femur, proximal tibia, or proximal humerus)
- radiographic findings: cartilage-capped bony spur on surface of bone ("mushroom" on x-ray)
- may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
- generally very slow growing and asymptomatic unless impinging on neurovascular structure ('painless mass')
  - growth usually ceases when skeletal maturity is reached
- malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)
- treatment: observation; surgical excision if symptomatic or concern for malignant transformation

Figure 58. T1 MRI of femoral enchondroma

Enchondroma
- benign hyaline cartilage growth; abnormality of chondroblasts, develops in medullary cavity
  - single/multiple enlarged rarefied areas in tubular bones
  - lytic lesion with sharp margination and irregular central calcification (stippled/punctate/popcorn appearance)
- majority asymptomatic, presenting as incidental finding or pathological fracture
- 2nd and 3rd decades
- 60% occur in the small tubular bones of the hand and foot; others in femur (20% - Figure 57), humerus, ribs
- radiographic findings: well-defined, lucent, central medullary lesions that calcify over time
- malignant degeneration to chondrosarcoma occurs in 1-2% (rest/nocturnal pain in absence of pathologic fracture is an important clue)
- treatment: observation with serial x-rays; surgical curettage if symptomatic or lesion grows

CYSTIC LESIONS

Unicameral/Solitary Bone Cyst
- most common cystic lesion; serous fluid-filled lesion with fibrous lining
- children and young adults, peak incidence during first 2 decades
- proximal humerus and femur most common
- symptoms: asymptomatic, or localized pain; complete pathological fracture (50% of presentations) or incidental detection
- radiographic findings: lytic translucent area on metaphyseal side of growth plate, cortex thinned/expanded; well-defined lesion
- treatment: observation with serial radiography 4-6 mo; if needed, aspiration followed by steroid injection; curettage ± bone graft indicated if structural integrity of bone is compromised

Figure 59. X-ray of aneurysmal bone cyst
Note the aggressive destruction of bone

Benign Aggressive Bone Tumours

Giant Cell Tumours/Aneurysmal Bone Cyst/Osteoblastoma
- affects patients of skeletal maturity, peak 3rd decade
- osteoblastoma: most commonly found in posterior elements of spine
- giant cell tumour: pulmonary metastases in 3%
- aneurysmal bone cysts: either solid with fibrous/granular tissue, or blood-filled
- radiographic findings
  - giant cell tumour: eccentric lytic lesions in epiphyses adjacent to subchondral bone; may break through cortex; T2 MRI enhances fluid within lesion (hyper-intense signal)
  - aneurysmal bone cyst: expansile, eccentric, and lytic lesion with bony septae ("bubbly appearance"); will have fluid-fluid levels on MRI
  - osteoblastoma: often nonspecific; calcified central nidus (>2 cm) with radiolucent halo and sclerosis
- symptoms: local tenderness and swelling, pain may be progressive (giant cell tumours), ± symptoms of nerve root compression (osteoblastoma)

Treatment
- intralesional curettage + bone graft or cement
- wide local excision of expendable bones
- recurrence rates of up to 20%

Figure 60. X-ray of osteosarcoma of distal femur

Malignant Bone Tumours

Table 26. Most Common Malignant Tumour Types for Age

Age	Tumour
<1	Neuroblastoma
1-10	Ewing's of tubular bones
10-30	Osteosarcoma, Ewing's of flat bones
30-40	Reticulum cell sarcoma, fibrosarcoma, periosteal osteosarcoma, malignant giant cell tumour, lymphoma
>40	Metastatic carcinoma, multiple myeloma, chondrosarcoma

Note: Although not a primary lesion, metastasis is one of the most common causes of malignancies in the elderly and should always be considered in the differential diagnosis and ruled in/out prior to surgical management

Osteosarcoma

- malignant bone tumour
- 2nd most common primary malignancy in adults after myeloma
- majority occur in 2nd decade of life, second peak in elderly patients with history of Paget's disease
- predilection for sites of rapid growth: distal femur (45% - *Figure 60, OR51*), proximal tibia (20%), and proximal humerus (15%)
  - invasive, variable histology; frequent metastases without treatment (lung most common)
- painful symptoms: progressive pain, night pain, poorly defined swelling, decreased ROM
  - radiographic findings: characteristic blastic and destructive lesion ("sunburst" pattern), periosteal reaction (Codman's triangle), soft tissue mass with maintenance of bone cortices; destructive lesion in metaphysis may cross epiphyseal plate
  - bone scan – rule out skeletal metastases; CT chest – rule out pulmonary metastases
- treatment: staging, neo-adjuvant chemotherapy, re-staging, limb salvage resection/reconstruction (rarely amputation), post-surgical neo-adjuvant chemotherapy
- prognosis: 90% survival for low-grade; 70% survival for high-grade

Chondrosarcoma

- malignant chondrogenic tumour
- primary (2/3 cases)
  - previous normal bone, patient >40 yr; expands into cortex to cause pain, pathological fracture
- secondary (1/3 cases)
  - malignant degeneration of pre-existing cartilage tumour such as enchondroma or osteochondroma
  - age range 25-45 yr, better prognosis than primary chondrosarcoma
- symptoms: progressive pain, uncommonly palpable mass or pathologic fracture
- radiographic findings: in medullary cavity, irregular "popcorn" calcification
- treatment: no role for neo-adjuvant chemotherapy or radiation; treat with wide surgical resection + reconstruction; regular follow-up x-rays of resection site and chest
- prognosis: 90% ten-year survival for low-grade; 29-55% survival for high-grade

Ewing's Sarcoma

- malignant, small round cell sarcoma; metastases frequent without treatment
- most occur between ages 5-25 yr
- florid periosteal reaction in metaphysis of long bone with diaphyseal extension
- signs/symptoms: presents with pain, fever, erythema, and swelling; anemia, increased WBC, ESR, LDH (mimics an infection)
- radiographic findings: destructive lesion with moth-eaten appearance and periosteal lamellated pattern ("onion-skinning")
- treatment: resection + chemotherapy ± radiation (can be treated solely with radiation in younger patients in select anatomic locations)
- prognosis: 70% survival; distant metastases significantly lower survival (<30%)

Multiple Myeloma

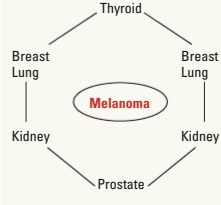
- proliferation of neoplastic plasma cells
- most common primary bone malignancy
- 90% occur in people >40 yr; M:F=2:1; twice as common in individuals of African descent
- signs/symptoms: localized bone pain (cardinal early symptom), compression/pathological fractures, renal failure, nephritis, high incidence of infections (e.g. pyelonephritis/pneumonia), systemic (weakness, weight loss, anorexia)
- labs: anemia, thrombocytopenia, increased ESR, hypercalcemia, increased Cr
- radiographic findings: multiple, "punched-out" well-demarcated lesions, no surrounding sclerosis, marked bone expansion
- diagnosis
  - serum/urine immunoelectrophoresis (monoclonal gammopathy)
  - CT-guided biopsy of lytic lesions at multiple bony sites

Figure 61. X-ray of femur chondrosarcoma

Signs of Hypercalcemia

"Bones, Stones, Moans, Groans, Psychiatric overtones"
CNS: headache, confusion, irritability, blurred vision
GI: N/V, abdominal pain, constipation, weight loss
MSK: fatigue, weakness, unsteady gait, bone and joint pain
GU: nocturia, polydipsia, polyuria, UTIs

Most Common Tumours Metastatic to Bone



BLT with a Kosher Pickle
Breast
Lung
Thyroid
Kidney
Prostate

- treatment
  - multiagent chemotherapy ± stem cell transplantation ± bisphosphonates
  - surgery for impending fractures: debulking, internal fixation
- prognosis: 5 yr survival 52%, prognosis increases with decreasing age
- see Hematology, H51

Bone Metastases

- most common cause of bone lesions in adults; typically age >40
- majority arise from breast or prostate; some arise from lung, thyroid, and kidney
- usually osteolytic lesions; prostate occasionally osteoblastic
- may present with mechanical pain and/or night pain, pathological fracture, hypercalcemia
- bone scan for MSK involvement; MRI if suspected spinal involvement
- treatment: pain control, bisphosphonates, surgical stabilization of impending fractures if Mirel's Critera >8

Table 27. Mirel's Criteria for Impending Fracture Risk and Prophylactic Internal Fixation

Variable	Number Assigned		
	1	2	3
Site	Upper arm	Lower extremity	Peritrochanteric
Pain	Mild	Moderate	Severe
Lesion	Blastic	Mixed	Lytic
Size	<1/3 bone diameter	1/3-2/3 diameter	>2/3 diameter

Common Medications

Table 28. Common Medications

Drug Name	Dosing Schedule	Indications	Comments
cefazolin (Ancef®)	1-2 g IV q8 h	Preoperative antibiotic prophylaxis	First generation cephalosporin; can be used with penicillin allergy (<10% cross-reactivity; significantly higher rates of SSI/PJI with alternative ABx)
LMWH dalteparin (Fragmin®) enoxaparin (Lovenox®)	5000 IU SC once daily 30-40 mg SC once daily to BID 2.5 mg SC once daily	DVT prophylaxis	Fixed dose, no monitoring, improved bioavailability, increased bleeding rates
oral anticoagulants dabigatran (Pradaxa®) rivaroxaban (Xarelto®) apixaban (Eliquis®)	110 mg PO x1 then 220 mg PO once daily 10 mg PO once daily 2.5 mg PO BID	DVT prophylaxis	Predictable, no monitoring, oral administration Reversal agents: idarucizumab (dabigatran) andexanet alfa (rivaroxaban, apixaban)
Aspirin (ASA)	81mg PO BID	DVT prophylaxis	Recent evidence suggests similar efficacy to LMWH and Rivaroxaban with better side effect profile (lower hematoma/stiffness in TJA)
tranexamic acid (TXA)	10-20 mg/kg IV Topical application to wound	Reduce perioperative blood loss and transfusion	No evidence for increase in thromboembolic events
acetaminophen (Tylenol®)	1000 mg PO q6 h or q8 h	Analgesia for pain control	Max dose up to 4000 mg every 24 h Higher doses can be hepatotoxic in susceptible individuals
ibuprofen (Advil®, Motrin®)	200-800 mg PO q6-8 h (max 3200 mg/d)	Analgesia for inflammatory pain (arthritis)	NSAID, may cause gastric erosion and bleeding; avoid if concurrent advanced renal disease
triamcinolone (Aristocort®) – an injectable steroid	0.5-1 mL of 25 mg/mL	Suspension (injected into inflamed joint or bursa); amount varies by joint size	Potent anti-inflammatory effect; increased pain for 24 h, rarely causes fat necrosis and skin depigmentation
naproxen (Aleve®, Naprosyn®)	250-500 mg BID	Analgesia for pain due to inflammation, arthritis, soft tissue injury	NSAID, may cause gastric erosion and bleeding; avoid if concurrent advanced renal disease
celecoxib (Celebrex®)	200 mg PO BID	Component of multimodal pain control and prophylaxis of HO after THA	NSAID (COX-2 inhibitor), cardiotoxic
indomethacin (Indocid®)	25 mg PO TID	Prophylaxis of HO after THA	Use with misoprostol

Landmark Orthopedic Trials

Trial Name	Reference	Clinical Trial Details
HEALTH	NEJM 2019; 381:2199-2208	**Title**: Total Hip Arthroplasty or Hemiarthroplasty for Hip Fracture **Purpose**: Despite being amongst the top 10 causes of disability in adults, there is still ambiguity in the treatment of displaced femoral neck fractures. **Methods**: 1495 patients who were ">50 yr and had a displaced femoral neck fracture were randomly assigned to have a total hip arthroplasty or hemiarthroplasty. **Results**: A secondary hip procedure within 24 months of follow-up occurred in 7.9% of the total hip arthroplasty and 8.3% of the hemiarthroplasty group. Hip instability occurred in 4.7% of the total hip arthroplasty, and 2.4% of the hemiarthroplasty group. Function was modestly better in total hip arthroplasty over hemiarthroplasty. **Conclusions**: The incidence of secondary procedures, and function over 24 months between the total hip arthroplasty and hemiarthroplasty group did not have a significant difference.
PROFHER	JAMA 2015 Mar 10;313(10):1037-47	**Title**: Surgical vs. Nonsurgical Treatment of Adults with Displaced Fractures of the Proximal Humerus: the PROFHER Randomized Clinical Trial **Purpose**: To evaluate the efficacy of surgical management in adults with displaced fractures of the proximal humerus involving the surgical neck. **Methods**: A randomized clinical trial where 260 patients, who presented to 32 UK hospitals after sustaining a displaced fracture of the proximal humerus involving the surgical neck were randomized into surgical and nonsurgical treatment groups, then followed for 2 yr. **Results**: No significant mean treatment group differences in Oxford Shoulder Score averaged over 2 yr (39.07 points for the surgical group vs. 38.32 points for the nonsurgical group; difference of 0.75 points [95% CI, -1.33 to 2.84 points]; P = .48). **Conclusions**: No significant differences between surgical treatment vs. non-surgical treatment. These results do not support the use of surgery for patients with displaced proximal humerus fractures involving the surgical neck.
FLOW	N Engl J Med 2015; 373:2629-2641	**Title**: A Trial of Wound Irrigation in the Initial Management of Open Fracture Wounds **Purpose**: To investigate the effects of castile soap versus normal saline irrigation delivered by means of high, low, or very low irrigation pressures. **Methods**: 2551 patients from 41 clinical centers, who had an open fracture of an extremity undergoing irrigation were randomly assigned to one of three irrigation pressures (high, low, and very low) and one of two irrigation solutions (castile soap versus normal saline). The primary outcome in this study was reoperation within 12 months after the initial surgery. **Results**: Hazard ratio showed no significant difference between the rates of reoperation within 12 months between the different irrigation pressures. Reoperation occurred in 14.8% in the soap group and in 11.6% in the saline group (hazard ratio, 1.32, 95% CI, 1.06 to 1.66; P=0.01). **Conclusions**: Rates of reoperation were similar regardless of irrigation pressure. The reoperation rate was higher in the soap group than in the saline group. These findings indicate low pressure saline irrigation is an acceptable form of wound irrigation.
A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee	N Engl J Med 2002; 347:81-88	**Title**: A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee **Purpose**: To compare evaluated the efficacy of arthroscopy for OA of the knee. **Methods**: A total of 180 patients with knee OA were randomized to receive arthroscopic debridement, arthroscopic lavage, or placebo surgery. Outcome measures included self-reported pain and function scales. **Results**: There was no statistically or clinically meaningful difference in pain or function scores at any point in time between patients receiving an arthroscopic intervention compared to placebo surgery. **Conclusions**: Arthroscopic debridement or arthroscopic lavage is no better than placebo surgery in improving pain and function in patients with knee OA.
PRONOMOS	N Engl J Med 2020; 382:1916-1925	**Title**: Rivaroxaban or Enoxaparin in Nonmajor Orthopedic Surgery **Purpose**: To compare the efficacy of rivaroxaban vs. enoxaparin in prevention of major venous thromboembolic events in nonmajor orthopedic surgery patients. **Methods**: This was a non-inferiority trial. A total of 3604 patients undergoing lower-limb nonmajor orthopedic surgery, who were at risk for venous thromboembolism, were randomized to receive rivaroxaban or enoxaparin. The primary outcome was a composite outcome of symptomatic distal or proximal deep vein thrombosis, pulmonary embolism, or venous thromboembolism-related death. **Results**: Major venous thromboembolism occurred in 0.2% of patients who received rivaroxaban, compared to 1.1% of patients in the enoxaparin group (risk ratio 0.25; 95% CI 0.09-0.75). There was no significant difference in incidence of bleeding between the groups. **Conclusions**: Rivaroxaban was more effective than enoxaparin in prevention venous thromboembolic events during the immobilization period after nonmajor orthopedic surgery.
OVIVA	N Engl J Med 2019; 380:425-436	**Title**: Oral versus Intravenous Antibiotics for Bone and Joint Infection **Purpose**: To determine whether oral antibiotic therapy is noninferior to intravenous antibiotic therapy for the management of complex orthopedic infections. **Methods**: A total of 1054 patients being treated for acute or chronic bone or joint infection were randomized to management with oral or intravenous antibiotics for the first six weeks of treatment. The primary outcome was definitive treatment failure within 1 year after randomization. **Results**: Treatment failure occurred in 14.6% of participants in the intravenous group and 13.2% of participants in the oral group. The difference in risk of -1.4% (95% CI -5.6-2.9) meets noninferiority criteria. **Conclusions**: Oral antibiotics were noninferior to intravenous antibiotics for the treatment of complex orthopedic infections in the first six weeks.

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OT Otolaryngology

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Acronyms

ABR	auditory brainstem response	CPAP	continuous positive airway pressure	HPV	human papillomavirus	PMN	polymorphonuclear leukocytes
AC	air conduction	CVA	cerebrovascular accident	HSV	herpes simplex virus	RA	rheumatoid arthritis
AOM	acute otitis media	EAC	external auditory canal	INCS	intranasal corticosteroids	RSV	respiratory syncytial virus
BAHA	bone-anchored hearing aid	ESS	endoscopic sinus surgery	MEE	middle ear effusion	SCC	squamous cell carcinoma
BC	bone conduction	EBV	Epstein-Barr virus	MEI	middle ear inflammation	SCM	sternocleidomastoid
BPPV	benign paroxysmal positional vertigo	FAP	familial adenomatous polyposis	MS	multiple sclerosis	SNHL	sensorineural hearing loss
CHL	conductive hearing loss	FNA	fine needle aspiration	OE	otitis externa	SRT	speech reception threshold
CMV	cytomegalovirus	GERD	gastroesophageal reflux disease	OM	otitis media	TEF	tracheoesophageal fistula
CNS	central nervous system	GPA	granulomatosis with polyangiitis	OME	otitis media with effusion	TM	tympanic membrane
CPA	cerebellopontine angle	H&N	head and neck	OPC	oropharyngeal cancer	TMJ	temporomandibular joint
		HL	hearing loss	OSA	obstructive sleep apnea	TMP-SMX	trimethoprim/sulfamethoxazole
				PFP	peripheral facial paralysis	URTI	upper respiratory tract infection

Basic Anatomy Review

Ear

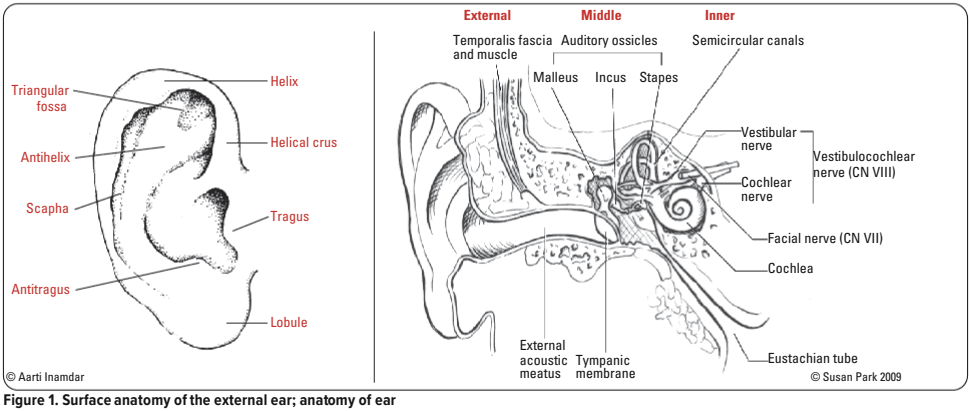

Figure 1. Surface anatomy of the external ear; anatomy of ear

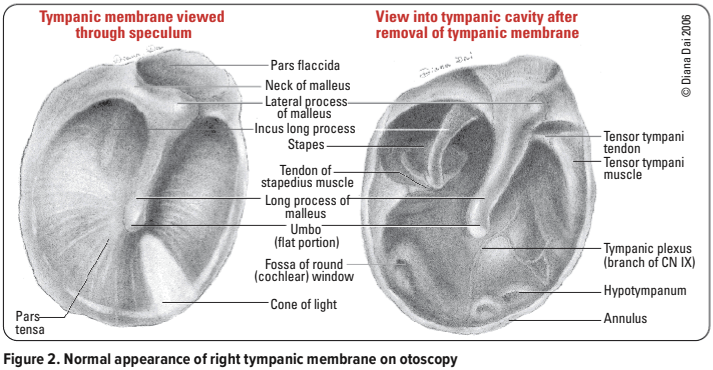

Figure 2. Normal appearance of right tympanic membrane on otoscopy

Nose

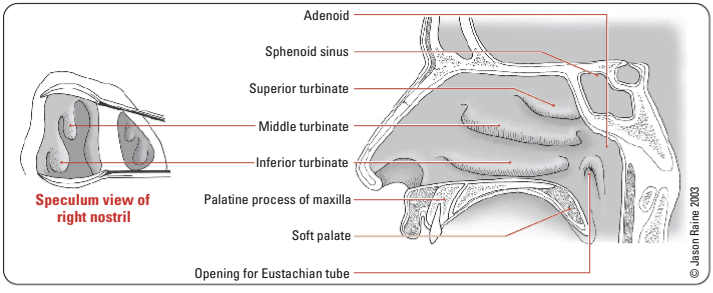

Figure 3. Nasal anatomy

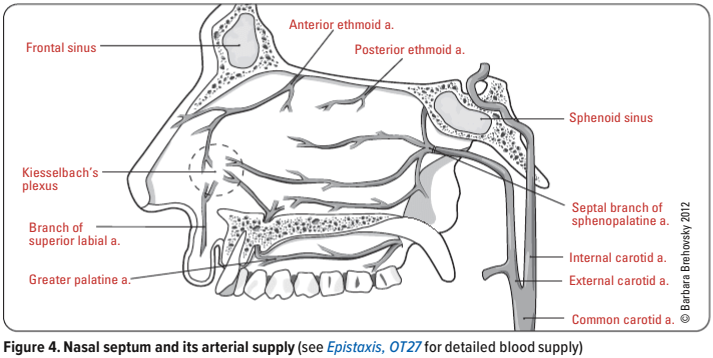

Figure 4. Nasal septum and its arterial supply (see *Epistaxis, OT27* for detailed blood supply)

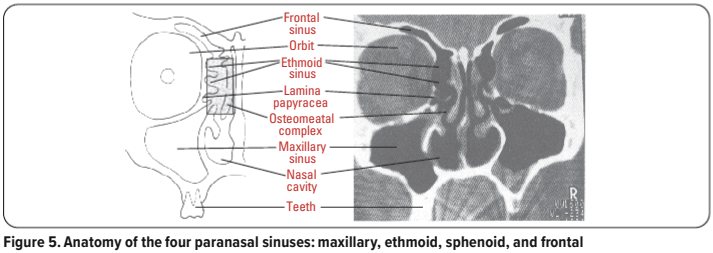

Figure 5. Anatomy of the four paranasal sinuses: maxillary, ethmoid, sphenoid, and frontal
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Throat

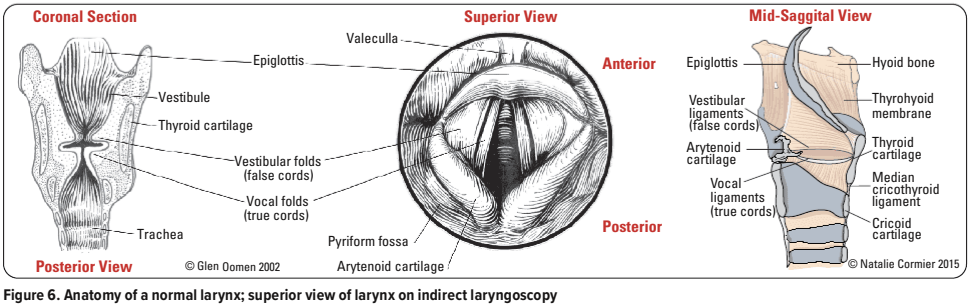


Figure 6. Anatomy of a normal larynx; superior view of larynx on indirect laryngoscopy

Head and Neck

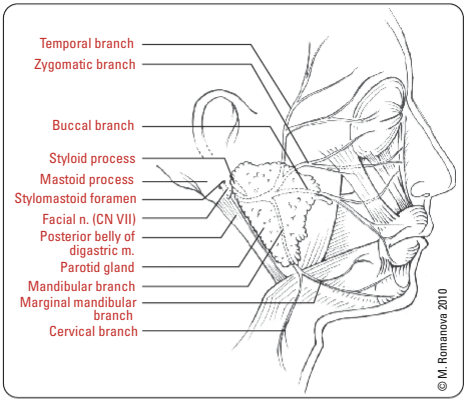


Figure 7. Extratemporal segment of facial nerve
Branches of facial nerve (in order from superior to inferior)
To Zanzibar **B**y **M**otor **C**ar

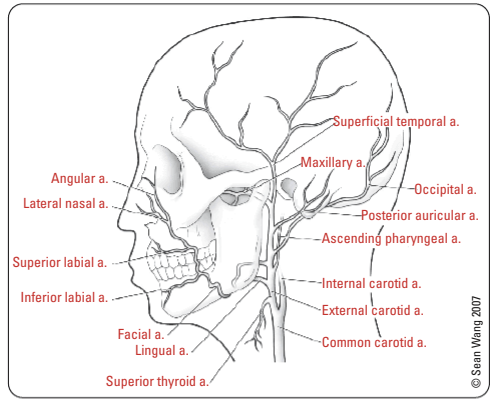


Figure 8. Blood supply to the face
Branches of the external carotid artery (in order from inferior to superior)
Some **A**natomists **L**ike **F**reaking **O**ut **P**oor **M**edical **S**tudents

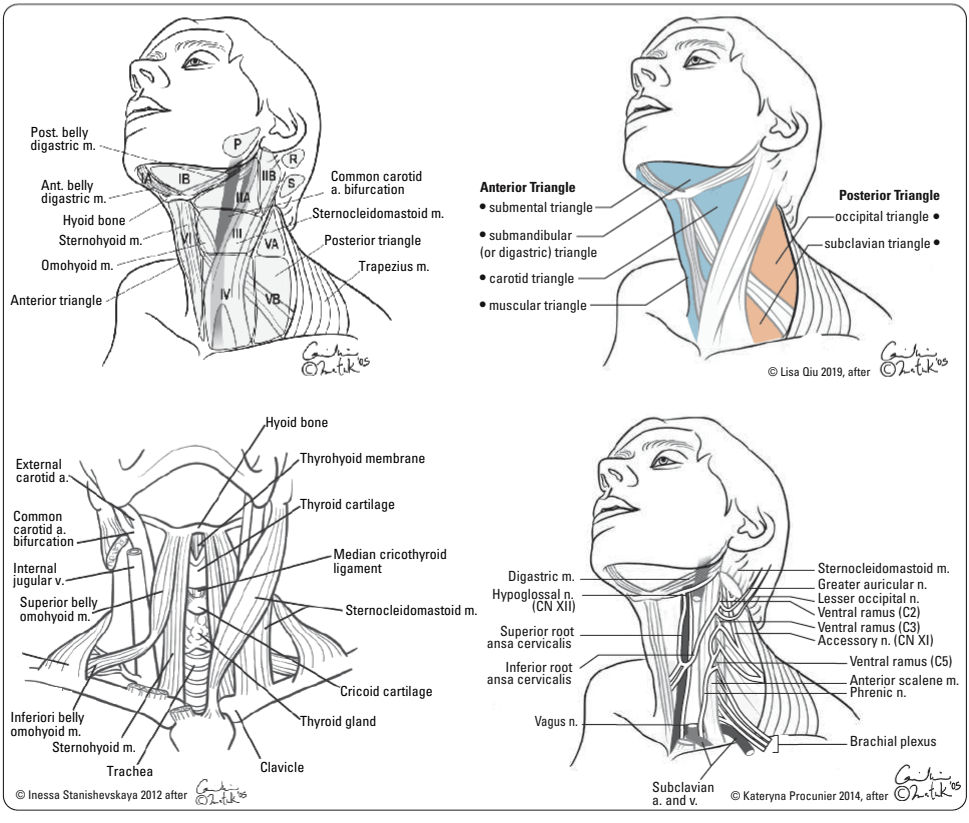


Figure 9. Anatomy of the neck

Anatomical Triangles of the Neck

Anterior triangle

- bound by anterior border of SCM, midline of neck from the jugular notch of the manubrium to the mentum, and lower border of mandible
- divided into:
  - **submental/suprahyoid triangle** (only unpaired triangle): bound by both anterior bellies of the digastric muscles from the mentum to the hyoid bone
  - **digastric/submandibular/submaxillary triangle:** bounded by anterior and posterior bellies of the digastric muscles and inferior border of mandible
  - **carotid triangle:** bounded by SCM, superior belly of the omohyoid muscles, and posterior belly of digastric muscles
    - contains: tail of parotid, submandibular gland, hypoglossal nerve, and carotid bifurcation
  - **muscular triangle**: bounded by SCM, superior belly of the omohyoid muscles, and midline of neck from the jugular notch of the manubrium to the hyoid bone
    - contains: internal jugular vein, vagus nerve

Posterior triangle

- bound by posterior border of the SCM, anterior border of trapezius, and middle third of clavicle
- divided into:
  - **occipital triangle**: superior to inferior belly of the omohyoid muscle
  - **subclavian triangle**: inferior to inferior belly of the omohyoid muscle
- contains: accessory nerve, roots/trunks of the brachial plexus, phrenic nerve, occipital and supraclavicular lymph nodes

Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of the Neck

Nodal Group/Level	Location	Drainage
1. Suboccipital (S)	Base of skull, posterior	Posterior scalp
2. Retroauricular (R)	Superficial to mastoid process	Scalp, temporal region, external auditory meatus, posterior pinna
3. Parotid-preauricular (P)	Anterior to ear	External auditory meatus, anterior pinna, soft tissue of frontal and temporal regions, root of nose, eyelids, palpebral conjunctiva
4. Submental (Level IA)	Anterior bellies (midline) of digastric muscles, tip of mandible, and hyoid bone	Floor of mouth, anterior tongue, anterior mandibular alveolar ridge, lower lip
5. Submandibular (Level IB)	Anterior belly of digastric muscles, stylohyoid muscle, body of mandible	Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland
6. Upper jugular (Levels IIA and IIB)	Skull base to inferior border of hyoid bone along SCM muscle	Oral cavity, nasal cavity, naso/oro/ hypopharynx, larynx, parotid glands
7. Middle jugular (Level III)	Inferior border of hyoid bone to inferior border of cricoid cartilage along SCM muscle	Oral cavity, naso/oro/hypopharynx, larynx
8. Lower jugular* (Level IV)	Inferior border of cricoid cartilage to clavicle along SCM muscle	Hypopharynx, thyroid, cervical esophagus, larynx
9. Posterior triangle (Levels VA and VB)**	Posterior border of SCM, anterior border of trapezius, from skull base to clavicle	Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck
10. Anterior compartment* (Level VI)**	Hyoid bone (midline) to suprasternal notch between the common carotid arteries	Thyroid gland, glottic- and subglottic larynx, apex of piriform sinus, cervical esophagus

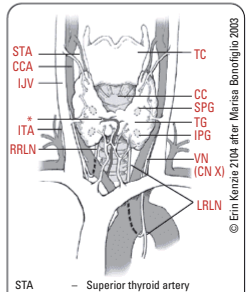
*Virchow's node: left lower jugular (level IV) supraclavicular node
**Includes some supraclavicular nodes
***Includes pretracheal, precricoid, paratracheal, and perithyroidal nodes

Paired Parasympathetic Ganglia of the Head and Neck
Ciliary (supplied by CN III): pupillary constriction
Pterygopalatine (supplied by CN VII): lacrimal gland, nasal mucosa
Submandibular (supplied by CN VII): submandibular, sublingual glands
Otic (supplied by CN IX): parotid glands

Functions of the Facial Nerve
"Ears, Tears, Face, Taste"
Ears: stapedius muscle, sensory around concha of auricle, EAC, and TM
Tears: lacrimation (lacrimal gland) and salivation (submandibular and sublingual glands)
Face: muscles of facial expression
Taste: sensory anterior ⅔ of tongue (via chorda tympani)

Lymphadenopathy
Left-sided enlargement of a supraclavicular node (Virchow's node) may indicate an abdominal malignancy or malignancy below the clavicle
Right-sided enlargement of a supraclavicular node may indicate malignancy of the mediastinum, lungs, or esophagus
Occipital and/or posterior auricular node enlargement may indicate rubella

4 Strap Muscles of the Neck
Thyrohyoid
Omohyoid
Sternohyoid
Sternothyroid



STA	–	Superior thyroid artery
CCA	–	Common carotid artery
IJV	–	Internal jugular vein
ITA	–	Inferior thyroid artery
RRLN	–	Right recurrent laryngeal nerve
TC	–	Thyroid cartilage
CC	–	Cricoid cartilage
SPG	–	Superior parathyroid gland
TG	–	Thyroid gland
IPG	–	Inferior parathyroid gland
VN (CN X)	–	Vagus nerve (CN X)
LRLN	–	Left recurrent laryngeal nerve

*Thyroidea ima artery: present in 3% of population, arises from aortic arch or innominate artery

Figure 10. Anatomy of the thyroid gland

Differential Diagnoses of Common Presentations

Dizziness

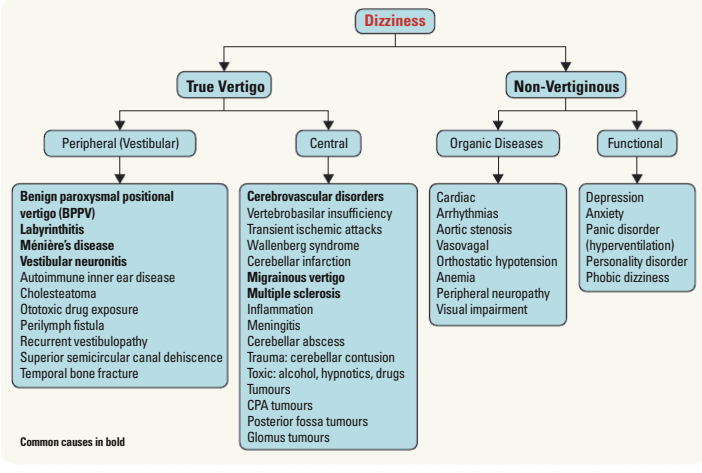


Figure 11. Differential diagnosis of dizziness

True nystagmus and vertigo caused by a peripheral lesion usually do not last longer than a few wk, due to compensation from the cerebellum (unless there is a history of cerebellar ischemia/stroke). Central lesions do not compensate, therefore nystagmus and vertigo will persist

Findings Suggestive of Central Vertigo

- Acute onset and continuous
- Normal head impulse test
- Multidirectional nystagmus
- Skew deviation present

5 Ds of Vertebrobasilar Insufficiency
Drop attacks
Diplopia
Dysarthria
Dizziness
Dysphagia

Otalgia

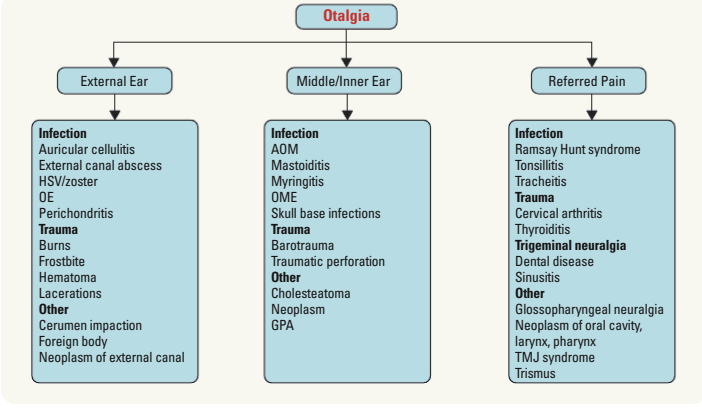


Figure 12. Differential diagnosis of otalgia

Otalgia – Referred Pain
Sensory innervation to the ear is supplied by CN V, VII, IX and X resulting in many sources of referred pain that can cause otalgia

The 10 Ts of Referred Pain which Cause Otalgia
Teeth: eustachian tube dysfunction, nasopharynx (area behind the nose, rule out tumour)
TMD: Temporomandibular Joint Disease
Tubal Area: Eustachian tube dysfunction, nasopharynx (area behind the nose (rule out tumour))
Tonsils: infections, tumours
Throat: infections, tumours of pharynx, larynx (voice box)
Tongue: inflammation, tumours
Trachea: (windpipe), Larynx (voice box)
Thyroid Gland: infections, tumours
Tempora Arteritis: inflammation of the artery above the ear
Trauma

Hearing Loss

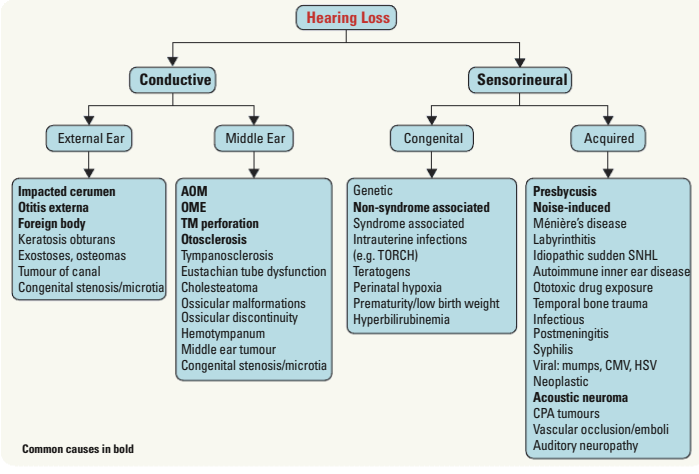


Figure 13. Differential diagnosis of hearing loss

Tinnitus

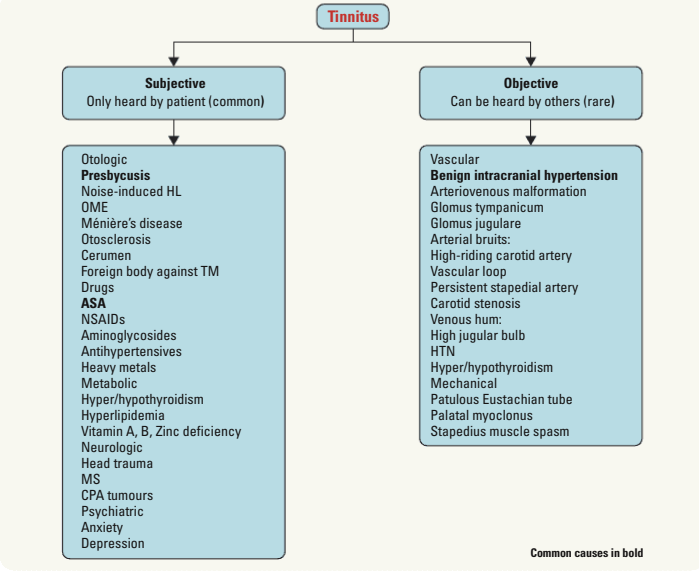


Figure 14. Differential diagnosis of tinnitus

Tinnitus is most commonly associated with SNHL

Glomus Tympanicum/Jugulare Tumour Signs and Symptoms

- Pulsatile tinnitus
- HL
- Blue mass behind TM
- Brown's sign (blanching of the TM with pneumatic otoscopy)

Nasal Obstruction

Table 2. Differential Diagnosis of Nasal Obstruction

	Acquired	Congenital
Nasal Cavity	Rhinitis (acute/chronic, vasomotor, allergic)	Pyriform aperture stenosis
	Rhinosinusitis	Choanal atresia
	Foreign bodies	Dermoid cyst
	Enlarged turbinates	Encephalocele
	Tumour	Glioma
	Benign: polyps, inverting papilloma (can become malignant)	
	Malignant	
	SCC	
	Esthesioneuroblastoma (olfactory neuroblastoma)	
	Adenocarcinoma	
	SCC	
	Esthesioneuroblastoma (olfactory neuroblastoma)	
	Adenocarcinoma	
Nasal Septum	Septal deviation	Septal deviation
	Septal dislocation	Septal dislocation
	Septal hematoma/abscess	Septal hematoma/abscess
	Juvenile nasopharyngeal angiofibroma (JNA)	
Nasopharynx	Adenoid hypertrophy	
	Tumour	
	Benign: polyps	
	Malignant: nasopharyngeal carcinoma	
Systemic	GPA, diabetes, vasculitis	

Hoarseness

Lung malignancy is the most common cause of extralaryngeal vocal cord paralysis

Table 3. Differential Diagnosis of Hoarseness

Infectious	Acute/chronic laryngitis Laryngotracheobronchitis (croup)	
Inflammatory	GERD Vocal cord polyps/nodules Lifestyle: smoking, chronic alcohol use	
Traumatic	External laryngeal trauma Endoscopy and endotracheal tube (e.g. intubation granuloma)	
Neoplastic	Benign tumour Papillomas (HPV infection) Minor salivary gland tumours Other	Malignant tumours (e.g. thyroid) SCC Other
Cysts	Retention cysts	
Systemic	Endocrine Hypothyroidism Virilization	Connective tissue disease RA SLE
Neurologic (vocal cord paralysis due to superior ± recurrent laryngeal nerve injury)	Central lesions CVA Head injury MS Skull base tumours Arnold-Chiari malformation Peripheral lesions Unilateral Lung malignancy	Iatrogenic injury: thyroid, parathyroid surgery, carotid endarterectomy, patent ductus arteriosus (PDA) ligation Bilateral Iatrogenic injury: bilateral thyroid surgery, forceps delivery Neuromuscular Myasthenia gravis
Functional	Psychogenic aphonia (hysterical aphonia)	
Congenital	Laryngomalacia Laryngeal web Laryngeal atresia	

Neck Mass

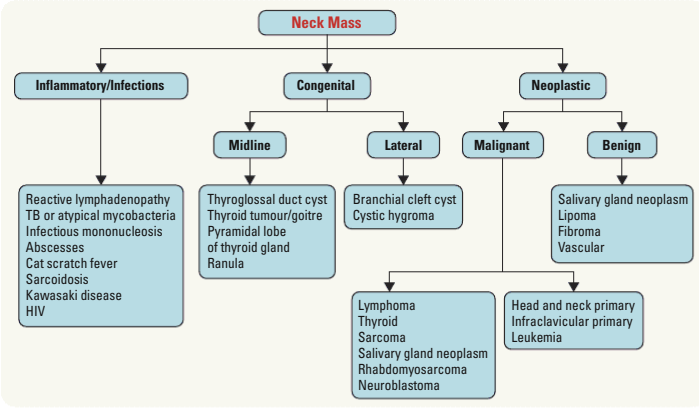


Figure 15. Differential diagnosis of a neck mass

Hearing

Normal Hearing Physiology

- conductive pathway (EAC to cochlea): AC of sound down the EAC → vibration of TM → sequential vibration of middle ear ossicles (malleus, incus, stapes) → transmission of amplified vibrations from the stapes footplate to the oval window of the cochlea → vibrations transmitted via cochlear fluid create movement along the basilar membrane within the cochlea
- neural pathway (nerve to brain): basilar membrane vibration stimulates overlying hair cells in the organ of Corti → stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII propagates the signal through → cochlear nucleus → superior olivary nucleus → lateral lemniscus → inferior colliculus → Sylvian fissure of temporal lobe

Order of the Neural Pathway (with Corresponding Waves on ABR)

E COLI
Eighth cranial nerve (I – II)
Cochlear nucleus (III)
Superior **O**livary nucleus
Lateral lemniscus (IV – V)
Inferior colliculus

Types of Hearing Loss

1. Conductive Hearing Loss

- conduction of sound to the cochlea is impaired
- can be caused by external and/or middle ear disease

2. Sensorineural Hearing Loss

- defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
- can be caused by disease of the inner ear (cochlea), cochlear/acoustic nerve (CN VIII), brainstem, or cortex

3. Mixed Hearing Loss

- combination of CHL and SNHL

Auditory Acuity

- whispered-voice test: mask one ear and whisper into the other
- tuning fork tests (see *Table 4, OT10*; audiogram is of greater utility)
  - Rinne test
    - 512 Hz tuning fork is struck and held firmly on mastoid process to test BC; the tuning fork is then placed beside the pinna to test AC
    - if AC > BC → positive Rinne (normal)
    - if BC > AC → negative Rinne (abnormal)
  - Weber test
    - 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative/does not lateralize) or is lateralized to one side (Weber right, Weber left)
    - can place vibrating fork on patient's chin while they clench their teeth, or directly on teeth to elicit more reliable response
    - will only lateralize if difference in HL between ears is >6 dB

Weber test lateralization = ipsilateral CHL or contralateral SNHL
The Weber test is more sensitive in detecting CHL than the Rinne test

Table 4. The Interpretation of Tuning Fork Tests

Examples	Weber	Rinne
Normal or bilateral SNHL	Central	AC>BC (+) bilaterally
Right-sided CHL, normal left ear	Lateralizes right	BC>AC (–) right
Right-sided SNHL, normal left ear	Lateralizes left	AC>BC (+) bilaterally
Right-sided severe SNHL or dead right ear, normal left ear	Lateralizes left	BC>AC (–) right*

*A vibrating tuning fork on the mastoid stimulates the cochlea bilaterally, therefore, in this case, the left cochlea is stimulated by the Rinne test on the right (e.g. a false negative test). These tests are not valid if the ear canals are obstructed with cerumen (e.g. will create conductive loss)

Frequency of Tuning Fork (Hz)	Minimum Hearing Loss for Rinne to Reverse (BC>AC, NEGATIVE Rinne) (dB)
256	15
512	30
1024	45

Pure Tone Audiometry

- a threshold is the lowest intensity level at which a patient can hear the tone 50% of the time
- thresholds are obtained for each ear at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz
- AC thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function
- BC thresholds are obtained with bone conduction oscillators, which bypass the outer and middle ear

Range of Frequencies Audible to Human Ear

20 to 20000 Hz

Most sensitive frequencies: 1000 to 4000 Hz

Range of human speech: 500 to 2000 Hz

Degree of Hearing Loss

- determined on basis of the pure tone average at 500, 1000, and 2000 Hz

HL occurs most often at higher frequencies. Noise-induced (occupational) HL is classically seen at 4000 Hz (Boilermaker's notch). HL associated with otosclerosis is seen at 2000 Hz (Carhart's notch)

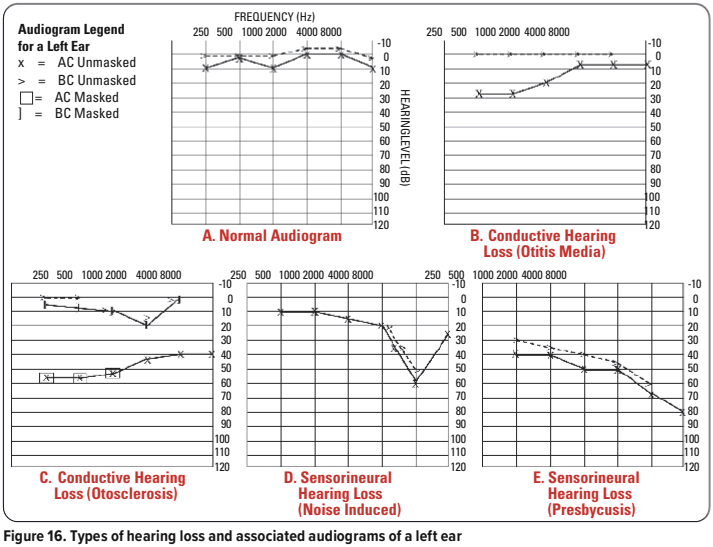

Audiogram Legend for a Left Ear
x = AC Unmasked
> = BC Unmasked
□ = AC Masked
] = BC Masked
FREQUENCY (Hz)
250 500 1000 2000 4000 8000
HEARING LEVEL (dB)
A. Normal Audiogram
B. Conductive Hearing Loss (Otitis Media)
C. Conductive Hearing Loss (Otosclerosis)
D. Sensorineural Hearing Loss (Noise Induced)
E. Sensorineural Hearing Loss (Presbycusis)

Figure 16. Types of hearing loss and associated audiograms of a left ear

PURE TONE PATTERNS

1. Conductive Hearing Loss (see Figures 16B and 16C)

- BC in normal range
- AC outside of normal range
- gap between AC and BC thresholds >10 dB (an air-bone gap)

2. Sensorineural Hearing Loss (see Figures 16D and 16E)

- both air and bone conduction thresholds below normal
- gap between AC and BC <10 dB (no air-bone gap)

3. Mixed Hearing Loss

- both air and bone conduction thresholds below normal
- gap between AC and BC thresholds >10 dB (an air-bone gap)

Speech Audiometry

Speech Reception Threshold

- lowest hearing level at which patient is able to repeat 50% of two syllable words that have equal emphasis on each syllable (spondee words)
- SRT and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB; if not, suspect a retrocochlear lesion or functional HL
- used to assess the reliability of the pure tone audiometry

Speech Discrimination Test

- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at 40 dB above the patient's SRT, therefore degree of HL is taken into account
- patients with normal hearing or CHL score >90%
- rollover effect: a decrease in discrimination as sound intensity increases; typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears, as asymmetry may indicate a retrocochlear lesion
- best predictor of hearing aid response: a poor discrimination score indicates significant neural degeneration and hearing aids may not be the best option for the patient

Impedance Audiometry

Tympanogram

- the Eustachian tube equalizes the pressure between the external and middle ear
- tympanograms graph the compliance of the middle ear system against a pressure gradient ranging from –400 to +200 mmH2O
- tympanogram peak occurs at the point of maximum compliance: where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range: –100 to +50 mmH2O

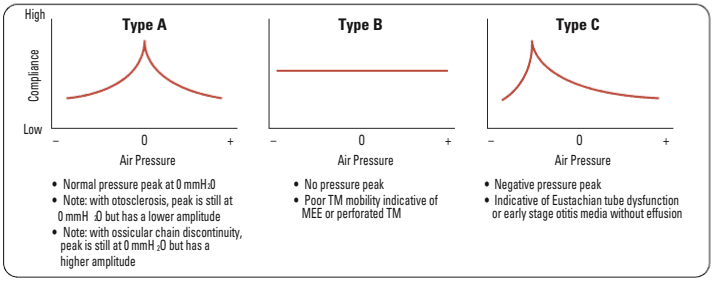

High
Compliance
Low
Type A
Type B
Type C
–
0
+
Air Pressure
• Normal pressure peak at 0 mmH2O
• Note: with otosclerosis, peak is still at 0 mmH2O but has a lower amplitude
• Note: with ossicular chain discontinuity, peak is still at 0 mmH2O but has a higher amplitude
• No pressure peak
• Poor TM mobility indicative of MEE or perforated TM
• Negative pressure peak
• Indicative of Eustachian tube dysfunction or early stage otitis media without effusion

Figure 17. Tympanograms

Static Compliance

- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0.3-1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of >2 cc in children and >2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

Acoustic Stapedial Reflexes

- stapedius muscle contracts in response to loud sound
- acoustic reflex threshold = 70-100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
  - stimulating either ear causes bilateral and symmetrical reflexes
  - for reflex to be present, CN VII must be intact with no CHL in monitored ear
  - if reflex is absent without CHL or severe SNHL, suspect CN VII lesion
- acoustic reflex decay test = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
  - normally, little reflex decay occurs at 500 and 1000 Hz
- with cochlear HL, acoustic reflex thresholds are 25-60 dB
- with retrocochlear HL (acoustic neuroma), absent acoustic reflexes or marked reflex decay (>50%) within 5 s

Auditory Brainstem Response

- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (see *Order of the Neural Pathway sidebar, OT9*; this test can be used to determine the site of lesion)
- delay in brainstem response suggests cochlear or retrocochlear abnormalities
- does not require volition or co-operation of patient (therefore, value retained in children and malingerers)

Otoacoustic Emissions

- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- signals come from outer hair cells which are a proxy for the inner hair cells which facilitate hearing
- often used in newborn screening
- can be used to uncover normal hearing in malingering patients
- absence of emissions can be due to HL, fluid in the middle ear, or narrow EACs

Prelingual deafness: deafness occurring before speech and language are acquired
Postlingual deafness: deafness occurring after speech and language are acquired

Aural Rehabilitation

- dependent on degree of HL, communicative requirements, motivation, expectations, and physical and mental abilities
- negative prognostic factors
  - poor speech discrimination
  - narrow dynamic range (recruitment)
  - unrealistic expectations
- types of hearing aids
  - BTE: behind-the-ear (with occlusive mould or open fit which allows natural sound to pass – for less severe hearing loss)
  - ITE: in-the-ear, placed in concha
  - ITC: in-the-canal, placed entirely in ear canal
  - CIC: contained-in-canal, placed deeply in ear canal
  - BAHA: bone-anchored hearing aid, attached to skull (bone conduction)
  - CROS: contralateral routing of signals
- assistive listening devices
  - direct/indirect audio output
  - infrared, FM radio, or induction loop systems
  - telephone, television, or alerting devices
- cochlear implants
  - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
  - for profound bilateral SNHL refractory to conventional hearing aids
  - established indication: postlingually deafened adults, pre- and postlingually deaf children

Prelingually deaf infants are the best candidates for aural rehabilitation because they have maximal benefit from ongoing developmental plasticity

BAHAs function are based on bone conduction and are indicated primarily for patients with CHL, unilateral HL, and mixed HL who cannot wear conventional hearing aids. BAHAs consist of an osseointegrated titanium implant, an external abutment, and a sound processor. The sound processor transmits vibrations through the external abutment to the titanium implant and then directly to the cochlea

Vertigo

Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
  - produced by peripheral (inner ear) or central (brainstem-cerebellum) stimulation
  - important to distinguish vertigo from other potential causes of "dizziness" (see *Figure 11, OT6*)

Table 5. Peripheral vs. Central Vertigo

Symptoms	Peripheral	Central
Imbalance	Moderate-severe	Mild-moderate
Nausea and Vomiting	Severe	Variable
Auditory Symptoms	Common	Rare
Neurologic Symptoms	Rare	Common
Compensation	Rapid	Slow
Nystagmus	Unidirectional Horizontal or rotatory	Bidirectional Horizontal or vertical

Table 6. HINTS (Head Impulse-Nystagmus-Test of Skew) Exam

Test	Central (Infarct)	Peripheral (Vestibular Neuritis)
Head Impulse	No saccades	Saccade present
Nystagmus	Nystagmus dominantly vertical, torsional, or gaze-evoked directional	Unidirectional, horizontal nystagmus
Test of Skew	Abnormal	Normal

Table 7. Differential Diagnosis of Vertigo Based on History

Condition	Time Course	Hearing Loss	Tinnitus	Aural Fullness	Other Features
Benign Paroxysmal Positional Vertigo (BPPV)	Seconds, recurrent	–	–	–	Onset with change in position
Ménière's Disease	min to h, episodic	Uni/bilateral, fluctuating	+	Pressure/warmth	
Labyrinthitis/ Vestibular Neuronitis	h to d	Unilateral	± Whistling	–	May have recent AOM
Acoustic Neuroma	Chronic	Progressive	+	–	Ataxia CN VII palsy
Brainstem/ Cerebellar Infarct	Prolonged	–	–	–	Suspect if vascular risk factors

Benign Paroxysmal Positional Vertigo

Definition
- acute attacks of transient rotatory vertigo lasting less than 1 min, initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)
- most common form of positional vertigo (50% of patients with peripheral vestibular dysfunction have BPPV)

Etiology
- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
  - can affect each of the 3 semicircular canals, although the posterior canal is affected in >90% of cases
  - caused by: head injury, viral infection (URTI), degenerative disease, idiopathic
  - results in slightly different signals being received by the brain from the two balance organs, resulting in sensation of movement

Diagnosis
- history (time course, provoking factors, associative symptoms)
- positive Dix-Hallpike maneuver (sensitivity 82%, specificity 71%)

Dix-Hallpike Positional Testing (see website for video and illustrations)
- the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45°, and neck extended 20°; hold the position for 20 s
- onset of vertigo and rotatory nystagmus indicate a positive test for the dependent side
- other diagnostic testing is not indicated in posterior canal BPPV

Treatment
- reassure patient that process resolves spontaneously
- particle repositioning maneuvers
  - Epley maneuver (performed by physician or by patient with the help of devices such as the DizzyFIX™)
  - Brandt-Daroff exercises (performed by patient)
- anti-emetics for N/V
- posterior semicircular canal occlusion or singular neurectomy for refractory cases
- drugs to suppress the vestibular system delay eventual recovery and are therefore not used

BPPV is the most common cause of episodic vertigo; patients are often symptomatic when rolling over in bed or moving their head to a position of extreme posterior extension (such as looking up at a tall building or getting their hair washed at the hairdresser)

Signs of BPPV Seen with Dix-Hallpike Maneuver
- Latency of ~20 s
- Crescendo/decrescendo vertigo lasting 20 s
- Geotropic rotatory nystagmus (nystagmus MUST be present for a positive test)
- Reversal of nystagmus upon sitting up
- Fatigability with repeated stimulation

Ménière's Disease (Endolymphatic Hydrops)

Definition
- episodic attacks of tinnitus, HL, aural fullness, and vertigo lasting min to h

Proposed Etiology
- inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth

Diagnostic Criteria for Ménière's Disease

Definite Ménière's Disease
- Two or more spontaneous episodes of vertigo lasting from 20 min to 12 h
- Audiometric confirmation of SNHL (low to mid frequency)
- Fluctuating tinnitus and/or aural fullness

Probable Ménière's Disease
- Two or more spontaneous episodes of vertigo or dizziness lasting from 20 min to 24 h
- Fluctuating tinnitus and/or aural fullness

Epidemiology
- peak incidence 40-60 yr
- bilateral in 35% of cases

Clinical Features
- episodic vertigo, fluctuating low frequency SNHL, tinnitus, and aural fullness, ± drop attacks (Tumarkin crisis), ± N/V
- vertigo disappears with time (min to h), but HL remains
- early in the disease: fluctuating SNHL
- later stages: persistent tinnitus and progressive HL
- attacks come in clusters and can be debilitating to the patient
- triggers: high salt intake, caffeine, stress, nicotine, and alcohol

Treatment
- acute management may consist of bed rest, antiemetics, antivertiginous drugs (e.g. betahistine (Serc®), meclizine, diphenhydramine), and anticholinergics (e.g. scopolamine)
- long-term management may include
  - medical
    - low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
    - Serc® prophylactically to decrease intensity of attacks
    - intratympanic gentamicin to destroy vestibular end-organ, results in complete SNHL
    - intratympanic glucocorticoids (e.g. dexamethasone) may improve vertigo symptoms
  - surgical
    - selective vestibular neurectomy or labyrinthectomy
    - potential benefit for endolymphatic sac decompression or sacculotomy
    - must monitor opposite ear, 35% of cases are bilateral

Vestibular Neuronitis (Labyrinthitis)

Definition
- acute onset of disabling vertigo often accompanied by N/V and imbalance without HL that resolves over days, leaving a residual imbalance that lasts d to wk
- vestibular neuronitis: inflammation of the vestibular portion of CN VIII
- labyrinthitis: inflammation of both vestibular and cochlear portions

Etiology
- thought to be due to a viral infection (e.g. measles, mumps, herpes zoster) or post-viral syndrome
- only ~30% of cases have associated URTI symptoms
- labyrinthitis may occur as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures

Clinical Features
- acute phase
  - severe vertigo with N/V and imbalance lasting 1-5 d
  - irritative nystagmus (fast phase towards the offending ear)
  - ataxia: patient tends to veer towards affected side
  - tinnitus and HL in labyrinthitis
- convalescent phase
  - imbalance and motion sickness lasting d to wk
  - spontaneous nystagmus away from affected side
  - gradual vestibular adaptation requires wk to mo

Drop Attacks (Tumarkin's Otolithic Crisis) are sudden falls occurring without warning and without loss of consciousness, where patient experiences feeling of being pushed down into the ground

Treatment
- acute phase
  - bed rest, antivertiginous drugs
  - corticosteroids (methylprednisolone) ± antivirals
  - bacterial infection: treat with IV antibiotics, drainage of middle ear, ± mastoidectomy
- convalescent phase
  - progressive ambulation, especially in the elderly
  - vestibular exercises: involve eye and head movements, sitting, standing, and walking

Before proceeding with gentamicin treatment, perform a gadolinium-enhanced MRI to rule out CPA tumour as the cause of symptoms

Acoustic Neuroma (Vestibular Schwannoma)

Definition
- schwannoma of the vestibular portion of CN VIII

Pathogenesis
- tumour starts in the internal auditory canal and expands into CPA, compressing cerebellum and brainstem
- when associated with type 2 neurofibromatosis: bilateral acoustic neuromas, juvenile cataracts, meningiomas, and ependymomas

Acoustic neuroma is the most common intracranial tumour causing SNHL and the most common CPA tumour

Clinical Features
- usually presents with unilateral SNHL (chronic) or tinnitus
- dizziness and unsteadiness may be present, but true vertigo is rare as tumour growth occurs slowly, allowing for compensation to occur
- facial nerve palsy and trigeminal (V1) sensory deficit (corneal reflex) are late complications
- risk factors: exposure to loud noise, childhood exposure to low-dose radiation, history of parathyroid adenoma

In the elderly, unilateral tinnitus or SNHL is acoustic neuroma until proven otherwise

Diagnosis
- MRI of internal auditory canal with gadolinium contrast (gold standard)
- audiogram (to assess SNHL)
- poor speech discrimination relative to the HL
- stapedial reflex absent or significant reflex decay
- ABR: increase in latency of the 5th wave
- vestibular tests: normal or asymmetric caloric weakness (an early sign)

Treatment
- expectant management if tumour is very small or in elderly
- definitive management is surgical excision
- other options: gamma knife, radiation

Tinnitus

Definition
- an auditory perception in the absence of an acoustic stimuli, likely related to loss of input into neurons in central auditory pathways, that results in abnormal firing

History
- subjective vs. objective (see *Figure 14, OT7*)
- pulsatile vs. nonpulsatile
- unilateral vs. bilateral
- associated symptoms: HL, vertigo, aural fullness, otalgia, otorrhea

Investigations
- physical examination: cranial nerve examination, otoscopy, auscultate for bruits over the neck, mastoid, and preauricular areas for pulsatile tinnitus
- audiology
- if pulsatile
  - CT or magnetic resonance angiogram and venogram of the H&N to rule out vascular abnormalities
- if nonpulsatile and unilateral
  - non-contrast MRI

Treatment
- if a cause is found, treat the cause (e.g. drainage of middle ear effusion, embolization, or excision of arteriovenous malformation)
- with no treatable cause: 15% will resolve, 20% will improve, 15% will worsen, 50% will remain the same
- primary and secondary prevention for SNHL (e.g. avoid high-volume music through headphones, ototoxic meds, smoking, high glycemic load, and hypercholesterolemia)
- conservative management (e.g. check zinc levels, improve sleep, reduce stress, reduce caffeine and alcohol consumption)
- if cause is deemed benign, recognize distress that patient may be experiencing and provide reassurance
- sound amplification (e.g. hearing aids, white noise, tinnitus instrument)
- pharmacotherapy (e.g. melatonin)
  - consider tricyclic antidepressants and SSRI if comorbidities include anxiety and depression
- tinnitus retraining therapy
- surgical management (rare)

Diseases of the External Ear

Cerumen Impaction

Etiology
- ear wax: a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

Risk Factors
- hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

Clinical Features
- CHL, tinnitus, fullness, itching, otalgia, discharge, odour, and cough

Treatment
- observation, cerumenolytic agents (water dissolves cerumen better than over-the-counter medications), irrigation, or manual removal

Cerumen impaction is the most common cause of CHL for those 15-50 y/o

Syringing

Indications
- Totally occlusive cerumen with pain, decreased hearing, or tinnitus

Contraindications
- Active infection
- Previous ear surgery
- Only hearing ear
- TM perforation

Complications
- OE
- TM perforation
- Trauma
- Pain
- Vertigo
- Tinnitus
- Otitis media

Method
- Establish that TM is intact
- Gently pull the pinna superiorly and posteriorly
- Using lukewarm water, aim the syringe nozzle upwards and posteriorly to irrigate the ear canal

Exostoses

Definition
- bony protuberances in the EAC composed of lamellar bone

Etiology
- possible association with swimming in cold water

Clinical Features
- usually an incidental finding
- can cause cerumen impaction or OE, if large

Treatment
- no Tx unless symptomatic (e.g. frequent OE, CHL)

Otitis Externa

Definition
- inflammation of EAC or auricle

Etiology
- bacterial (90% of OE): Pseudomonas aeruginosa, Pseudomonas vulgaris, Escherichia coli, Staphylococcus aureus
- fungal: Candida albicans, Aspergillus niger

Risk Factors
- anatomic abnormalities: canal stenosis, exostoses, hairy ear canal
- canal obstruction: cerumen, foreign body, sebaceous cyst
- epithelial integrity: cerumen removal, earplugs, hearing aids, instrumentation/itching
- dermatologic conditions: eczema, psoriasis, seborrhea
- water in ear canal: swimming, other prolonged water exposures

Clinical Features
- acute
  - otalgia, itching, fullness, ± HL, ± ear canal pain on chewing
  - tenderness aggravated by traction of pinna or pressure over tragus
  - ear canal edema, erythema, ± otorrhea, ± regional lymphadenitis, ± cellulitis of the pinna
- chronic
  - pruritus of external ear ± excoriation of ear canal
  - atrophic and scaly epidermal lining, ± otorrhea, ± HL
  - wide meatus, but no pain with movement of auricle
  - TM appears normal

Pulling on the pinna is extremely painful in OE, but is usually well tolerated in otitis media

Treatment
- microdebridement
- topical antimicrobials, topical antibiotics ± topical corticosteroids
  - antipseudomonal agents (e.g. ciprofloxacin) or a combination therapy (e.g. Ciprodex®)
  - ototoxic topical agents (e.g. gentamicin, neomycin, neomycin/polymyxin B/hydrocortisone) should not be used in a perforated TM

- keep the EAC dry
- oral antibiotics if the infection has spread beyond the ear canal
- ± analgesics for pain management
- chronic OE: treat the underlying cause (e.g. dermatologic conditions)

Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

Definition
- osteomyelitis of the mastoid or temporal bone

Epidemiology
- occurs in elderly patients with DM and immunocompromised patients

Etiology
- rare complication of OE
- most commonly caused by Pseudomonas aeruginosa

Clinical Features
- otalgia and purulent otorrhea that is refractory to medical therapy
- granulation tissue or necrotic tissue on the floor of the auditory canal

Complications
- cranial nerve palsy (most commonly CN VII>CN X>CN XI)
- systemic infection, death

Management
- imaging: high resolution temporal bone CT scan, gadolinium-enhanced MRI, technetium scan
- medical emergency: hospitalization, debridement, IV antibiotics
- may require OR for debridement of necrotic tissue/bone

Gallium and Technetium Scans
Gallium scans are used to show sites of active infection. Gallium is taken up by PMN, and therefore only lights up when active infection is present. It will not show the extent of osteomyelitis. Technetium scans provide information about osteoblastic activity and, as a result, are used to demonstrate sites of osteomyelitis. Technetium scans help with Dx, whereas gallium scans are useful in follow-up

Diseases of the Middle Ear

Acute Otitis Media and Otitis Media with Effusion

- see *Pediatric Otolaryngology, OT39*

Chronic Otitis Media

Definition
- an ear with TM perforation in the setting of recurrent or chronic ear infections

Benign
- dry TM perforation without active infection

Chronic Serous Otitis Media
- continuous serous drainage (straw-coloured)

Chronic Suppurative Otitis Media
- persistent purulent drainage through a perforated TM

Cholesteatoma

Definition
- a cyst composed of keratinized desquamated epithelial cells occurring in the middle ear, mastoid, and temporal bone
- two types: congenital and acquired

Congenital
- presents as a "small white pearl" behind an intact TM (anterior and medial to the malleus) or as CHL
- believed to be due to aberrant migration of external canal ectoderm during development
- not associated with otitis media or Eustachian tube dysfunction

Acquired (more common)
- primary cholesteatoma
  - frequently associated with retraction pockets in the pars flaccida, pars tensa, or both
  - a sequela of the dysfunction of the regulation of middle ear pressure
  - often has crusting or desquamated debris on lateral surface
- secondary cholesteatoma
  - presents as "pearly mass" evident behind TM, frequently associated with marginal perforation
  - may appear as skin that has replaced the mucosa of the middle ear
- the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

Mechanisms of Cholesteatoma Formation
- Metaplasia of middle ear epithelium or basal cell hyperplasia (congenital)
- Invagination of TM (1° acquisition)
- Epithelial migration through TM perforation (2° acquisition)

Clinical Features
- history of otitis media (especially if unilateral), ventilation tubes, ear surgery
- symptoms
  - progressive HL (predominantly conductive, although may get SNHL in late stage)
  - otalgia, aural fullness, fever
- signs
  - retraction pocket in TM, may contain keratinous debris
  - TM perforation
  - granulation tissue, polyp visible on otoscopy
  - malodourous, unilateral otorrhea

Complications

Table 8. Complications of Cholesteatoma

Local	Intracranial
Ossicular erosion: CHL	Meningitis
Inner ear erosion: SNHL, dizziness, and/or labyrinthitis	Sigmoid sinus thrombosis
Temporal bone infection: mastoiditis, petrositis	Intracranial abscess (subdural, epidural, cerebellar)
Facial paralysis	

Investigations
- audiogram and non-contrast CT of temporal bones

Treatment
- surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction

Mastoiditis

Definition
- infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two wk after onset of untreated or inadequately treated AOM (suppurative)
- more common in children than adults

Classic Triad
- Otorrhea
- Tenderness to pressure over the mastoid
- Retroauricular swelling with protruding ear

Etiology
- acute mastoiditis is caused by the same organisms as AOM: *S. pneumoniae, H. influenzae, M. catarrhalis, S. pyogenes, S. aureus, P. aeruginosa*, etc.

Complications of AOM are rare due to rapid and effective treatment of AOM with antibiotics

Clinical Features
- otorrhea
- tenderness to pressure over the mastoid
- retroauricular swelling with protruding ear
- fever, HL, ± TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)

Treatment
- IV antibiotics with myringotomy and ventilation tubes – usually all that is required in acute cases
- may require additional incision and drainage of postauricular abscess
- cortical mastoidectomy
  - debridement of infected tissue allowing aeration and drainage
- indications for surgery
  - failure of medical treatment after 48 h
  - symptoms of intracranial complications
  - aural discharge persisting for 4 wk and resistant to antibiotics

Otosclerosis

Definition
- fusion of stapes footplate to oval window such that it cannot vibrate

Etiology
- autosomal dominant, variable penetrance approximately 40%
- F>M, progresses during pregnancy (hormone responsive)

Clinical Features
- progressive CHL first noticed in teens and 20 s (may progress to SNHL if cochlea involved)
- ± nonpulsatile tinnitus
- TM normal ± pink blush (Schwartz's sign) associated with the neovascularization of otosclerotic bone
- characteristic dip at 2000 Hz (Carhart's notch) on audiogram (see *Figure 16C, OT10*)

Treatment
- monitor with serial audiograms if coping with loss
- hearing aid (BAHA)
- stapedectomy or stapedotomy (using laser or drill) with prosthesis is definitive treatment

Otosclerosis is the 2nd most common cause of CHL in 15-50 y/o (after cerumen impaction)

Diseases of the Inner Ear

Congenital Sensorineural Hearing Loss

Hereditary Defects
- non-syndrome associated (70%)
  - often idiopathic, autosomal recessive
  - connexin 26 (GJB2 gene) most common
- syndrome associated (30%)
  - Waardenburg: white forelock, heterochromia iridis (differently coloured eyes), wide nasal bridge, and increased distance between medial canthi
  - Pendred: euthyroid goiter, SLC26A4 gene, enlarged vestibular aqueducts
  - Treacher-Collins: first and second branchial cleft anomalies
  - Alport: hereditary nephritis

Risk Factors
- family history of permanent HL
- craniofacial abnormality
- prenatal infections
  - TORCH: toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, CMV, HSV
  - Zika
- postnatal infections
  - bacterial meningitis, mumps, measles
- neonatal intensive care unit stay >2 d
- extracorporeal membrane oxygenation at birth
- assisted ventilation at birth/perinatal anoxia, birth trauma (hemorrhage into inner ear)
- ototoxic drug use
- hyperbilirubinemia requiring exchange transfusion

Treatment
- presence of any risk factor: ABR study performed before leaving NICU and at 3 mo adjusted age
- early rehabilitation improves speech and school performance

Presbycusis

Definition
- SNHL associated with aging (starting in 5th and 6th decades of life)

Etiology
- hair cell degeneration
- age-related degeneration of basilar membrane, possibly genetic etiology
- cochlear neuron damage
- ischemia of inner ear

Clinical Features
- progressive, bilateral hearing deterioration initially at high frequencies, followed by middle and lower frequencies
- loss of discrimination of speech, especially with background noise present – patients describe people as mumbling

Presbycusis is the most common cause of SNHL

- recruitment phenomenon: inability to tolerate loud sounds
- tinnitus

Treatment
- hearing aid if patient has difficulty functioning, HL >30-35 dB, and good speech discrimination
- ± lip reading, auditory training, auditory aids (doorbell and phone lights)

Sudden Sensorineural Hearing Loss

Etiology
- usually idiopathic (80-90% of cases); rule out other causes
  - autoimmune
  - infectious (e.g. EBV, group A Streptococcus, HSV, herpes-zoster virus, HIV, Lyme disease, meningitis, syphilis)
  - trauma
  - vascular (e.g. cerebrovascular disease)
  - neoplastic (e.g. angioma, meningioma, neurofibromatosis type 2, schwannoma)
  - other (e.g. ototoxins, pregnancy)

Sudden SNHL may easily be confused with ischemic brain events. It is important to keep a high index of suspicion especially with elderly patients presenting with sudden SNHL, as well as vertigo

Clinical Features
- presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, vertigo, aural fullness

Treatment
- treat the underlying cause
- MRI to rule out tumour and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)
- if idiopathic: intratympanic or oral corticosteroids (prednisone 1 mg/kg/d for 7-14 d). Start within 3 d (most ideal) up to 14 d after onset

Clinical Practice Guideline: Sudden Hearing Loss
Otolaryngol Head Neck Surg 2019 Aug;161
Recommendations Based on Findings:
- Confirm HL is sensorineural with audiometric testing (loss of at least 30 dB affecting three consecutive frequencies)
- Routine labs, CT, or MRI not required unless indicated by history and physical
- Initiate steroid treatment within 14 d of symptom onset

Prognosis
- depends on degree of HL
- 70% resolve within 10-14 d
- 20% experience partial resolution
- 10% experience permanent HL

Autoimmune Inner Ear Disease

Etiology
- idiopathic
- may be associated with systemic autoimmune diseases (e.g. RA, SLE), vasculitides (e.g. GPA, polyarteritis nodosa), and allergies

Epidemiology
- most common between ages 20-50

Clinical Features
- rapidly progressive or fluctuating bilateral SNHL
- ± tinnitus, aural fullness, vestibular symptoms (e.g. ataxia, disequilibrium, vertigo)

Investigations
- autoimmune workup: CBC, ESR, ANA, rheumatoid factor

Treatment
- high-dose corticosteroids: treat early for at least 30 d
- consider cytotoxic medication for steroid non-responders

Drug Ototoxicity

Aminoglycosides
- streptomycin and gentamicin (vestibulotoxic), kanamycin and tobramycin (cochleotoxic)
- toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
- destroys sensory hair cells: outer first, inner second (therefore, otoacoustic emissions are lost first)
- high frequency HL develops earliest
- ototoxicity occurs d-wk post-treatment
- must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
- q24 h dosing recommended (with amount determined by creatinine clearance)

- aminoglycoside toxicity displays saturable kinetics, therefore, once daily dosing presents less risk than divided daily doses
- duration of treatment is the most important predictor of ototoxicity
  - treatment: immediately stop aminoglycosides

Analgesics and Antipyretics
- acetaminophen, NSAIDs, and salicylates
- HL with tinnitus, reversible if discontinued

Others
- antineoplastic agents (e.g. bleomycin)
- loop diuretics (e.g. furosemide) and antimalarials (e.g. quinine)
  - reversible by decreasing or stopping medications

Noise-Induced Sensorineural Hearing Loss

Pathogenesis
- 85-90 dB over mo or yr, single sound impulses >135 dB, or repetitive vibratory insults (e.g. jackhammer) can cause cochlear damage
- bilateral SNHL initially and most prominently at 4000 Hz (resonant frequency of the temporal bone), known as "boilermaker's notch" on audiogram, extends to higher and lower frequencies with time (see *Figure 16D, OT10*)
- speech reception not altered until HL >30 dB at speech frequency, therefore considerable damage may occur before patient complains of HL
- difficulty with speech discrimination, especially in situations with competing noise

Phases of Hearing Loss
- dependent on: intensity of sound and duration of exposure
  - temporary threshold shift
    - when exposed to loud sound, decreased sensitivity, or increased threshold for sound
    - may have associated aural fullness and tinnitus
    - hearing returns to normal with removal of noise
  - permanent threshold shift
    - hearing does not return to previous state

Treatment
- hearing aid
- prevention
  - ear protectors: muffs, plugs
  - limit exposure to noise with frequent rest periods
  - regular audiologic follow-up

Temporal Bone Fractures

Table 9. Features of Temporal Bone Fractures

	Otic Capsule Involving (1)	Otic Capsule Sparing (2)
Extension	Into bony labyrinth and internal auditory meatus	Into middle ear
Incidence	10-20%	70-90%
Etiology	Frontal/occipital trauma	Lateral skull trauma
CN Pathology	CN VII palsy (50%)	CN VII palsy (10-20%)
Hearing Loss	SNHL due to direct cochlear injury	CHL 2° to ossicular injury
Vestibular Symptoms	Sudden onset vestibular symptoms due to direct semicircular canal injury (vertigo, spontaneous nystagmus)	Rare
Other Features	Intact external auditory meatus, TM ± hemotympanum Spontaneous nystagmus CSF leak in Eustachian tube to nasopharynx ± rhinorrhea (risk of meningitis)	Torn TM or hemotympanum Bleeding from EAC Step formation in EAC CSF otorrhea Battle's sign = mastoid ecchymosis Raccoon eyes = periorbital ecchymosis

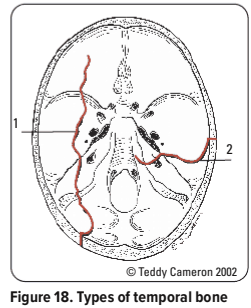


Figure 18. Types of temporal bone fractures

- characterized as longitudinal or transverse relative to the long axis of the petrous temporal bone
- temporal bone fractures are rarely purely transverse or longitudinal (often a mixed picture)

Diagnosis
- otoscopy
  - do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
- CT of temporal bones
- audiology, facial nerve tests (for transverse fractures), Schirmer's test (of lacrimation), stapedial reflexes if CN VII palsy
- if suspecting CSF leak: look for halo sign, send fluid for β-2 transferrin or β-trace protein (prostaglandin D synthase)

Signs of Basilar Skull Fracture
- Battle's sign (bruising over mastoid)
- Racoon eyes (periorbital ecchymosis)
- CSF rhinorrhea/otorrhea
- Hemotympanum (blood in the tympanic cavity of the middle ear)
- Cranial nerve involvement:
  - facial palsy → CN VII
  - nystagmus → CN VI
  - facial numbness → CN V

Treatment
- ABCs
- medical: expectant, prevent otogenic meningitis
- surgical: explore temporal bone; indications:
  - CN VII palsy (immediate and complete)
  - gunshot wound
  - depressed fracture of external auditory meatus
  - early meningitis (mastoidectomy)
  - bleeding intracranially from sinus
  - CSF otorrhea (may resolve spontaneously)

Complications
- AOM ± labyrinthitis ± mastoiditis
- meningitis/epidural abscess/brain abscess
- post-traumatic cholesteatoma

Facial Nerve (CN VII) Paralysis

Central Facial Paralysis
- (see Neurology, N3)

Peripheral Facial Paralysis
- mononeuropathy of the facial nerve characterized by weakness in the muscles of facial expression
- classified as primary if idiopathic or secondary if ascribed etiology

KITTENS acronym for DDx of Facial Nerve Palsy

(K) Congenital
Infection/Idiopathic
Trauma/toxins
Tumour
Endocrine
Neurologic
Systemic

Etiology
- congenital
- infection (e.g. otitis media, mastoiditis, HSV, varicella-zoster virus)
- idiopathic (Bell's Palsy)
- trauma
- toxins/drugs
- tumour
- endocrine (diabetes, preeclampsia, hyperthyroidism)
- neurologic (e.g. Guillain-Barré syndrome, myasthenia gravis, stroke, multiple sclerosis)
- systemic (e.g. sarcoidosis, amyloidosis, hyperostoses)

Think neoplasm rather than Bell's palsy if:
- Slow, progressive onset
- Involvement of other cranial nerves or presence of lateralizing signs (e.g. hemiparesthesias, hemiparalysis, aphasia)
- Sparing of frontalis (central palsy) vs. involvement of frontalis (peripheral palsy)
- Palpable mass over parotid gland in middle ear
- Adult with unilateral middle ear effusion

Treatment
- treat according to etiology; provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, upper eyelid weighted implants
- if idiopathic, corticosteroids ± antivirals in patients with severe to complete paresis
- facial paralysis that does not resolve with time or with medical treatment will often be referred for reanimation techniques to restore function
  - common reanimation techniques include:
    - direct facial nerve anastomosis
    - interpositional grafts
    - anastomosis to other motor nerves
    - muscle transpositions

Table 10. Bell's Palsy vs. Ramsay Hunt Syndrome

Etiology	Incidence	Findings	Investigations	Treatment, Follow-up, and Prognosis (Px)
Bell's Palsy Idiopathic, possible (HSV) infection involving CN VII Diagnosis of exclusion	80-90% of PFP **Risk Factors:** DM Pregnancy Past history	**Hx** Acute onset ± viral-like prodrome Postauricular pain Hyperacusis (30%) Decreased lacrimation **P/E** Paralysis or paresis of all muscle groups on one side of the face Absence of signs of CNS disease, upper motor neuron lesion, or CVA	Stapedial reflex absent Audiology normal (or baseline) EMG — best measure for prognosis Topognostic testing MRI with gadolinium — enhancement of CN VII and VIII High resolution CT	**Rx** Prevent exposure keratitis with patching or tarsorrhaphy Systemic steroids may lessen degeneration and hasten recovery Consider antiviral (acyclovir) **F/U** Spontaneous remission should begin within 3 wk of onset Delayed (3-6 mo) recovery portends at least some functional loss **Px** >90% + no voluntary EMG motor unit potentials = consider surgical decompression Poorer if hyperacusis, >60 yr, DM, HTN, severe pain, complete facial paralysis
Ramsay Hunt Syndrome (Herpes Zoster Oticus) Varicella zoster infection of CN VII/VIII	4.5-9% of PFP **Risk Factors:** 60 yr Impaired immunity Cancer Radiotherapy Chemotherapy	**Hx** Hyperacusis SNHL Severe pain of pinna, mouth, or face **P/E** Vesicles on pinna, external canal (erupt 3-7 d after onset of pain) Associated herpes zoster ophthalmicus (uveitis, keratoconjunctivitis, optic neuritis, or glaucoma)	Stapedial reflex absent Audiology — SNHL Viral ELISA studies to confirm MRI with gadolinium (86% of facial nerves enhanced)	**Rx** Avoid touching lesions to prevent spread of infection Systemic steroids can relieve pain, vertigo, avoid postherpetic neuralgia Acyclovir may lessen pain, aid healing of vesicles **F/U:** 2-4 wk **Px** Worse prognosis than Bell's palsy; 22% recover completely, 66% incomplete paralysis, 10% complete paralysis
Iatrogenic		Variable (depending on level of injury)	Wait for lidocaine to wear off EMG	**Rx** Exploration if complete nerve paralysis No exploration if any movement present

Rhinitis

Definition

- inflammation of the lining (mucosa) of the nasal cavity

Table 11. Classification of Rhinitis

Inflammatory	Non-Inflammatory

Perennial non-allergic
  Asthma, ASA sensitivity
Allergic (seasonal vs. perennial)
Atrophic
  Primary: *Klebsiella ozena* (especially in elderly)
  Acquired: post-surgery if too much mucosa or turbinate has been resected
Infectious
  Viral: rhinovirus, influenza, parainfluenza, etc.
  Bacterial: *S. aureus*
  Fungal
  Granulomatous: TB, syphilis, leprosy
Non-infectious (e.g. sarcoidosis, GPA)
Irritant (e.g. dust, chemicals, pollution)
	Rhinitis medicamentosa
	  Topical decongestants
	Hormonal
	  Pregnancy
	  Estrogens
	  Thyroid
	Idiopathic vasomotor

Rhinitis medicamentosa: rebound congestion due to the overuse of intranasal vasoconstrictors; limit use to no more than 3-5 d. Treat with saline irrigations and intranasal steroid

Table 12. Nasal Discharge: Character and Associated Conditions

Character	Associated Conditions
Watery/Mucoid	Allergic, viral, vasomotor, CSF leak (halo sign)
Mucopurulent	Bacterial, foreign body
Serosanguinous	Neoplasia
Bloody	Trauma, neoplasia, bleeding disorder, HTN/vascular disease

Allergic Rhinitis (i.e. Hay Fever)

Congestion reduces nasal airflow and allows the nose to repair itself (i.e. washes away the irritants). Treatment should focus on the initial insult rather than target this defense mechanism

Definition
- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds

Etiology
- IgE antibody mediated hypersensitivity reaction of the respiratory mucosa upon exposure to allergen
- concentration of allergen in the ambient air correlates with the rhinitis symptoms

Epidemiology
- age at onset usually <20 yr
- personal or family history of atopic disease

Clinical Features
- nasal congestion, nasal itch, watery rhinorrhea, sneezing, and hyposmia
- ± allergic conjunctivitis (redness, tearing, itching of the eyes)
- seasonal
  - caused by pollen from trees, grass, and ragweed
  - occurs during a specific season
- perennial
  - caused by airborne dust mite fecal particles, cockroach residues, animal dander, moulds, and tobacco smoke
  - occurs throughout the yr

Complications
- chronic sinusitis/polyps
- serous otitis media

Diagnosis
- history
- physical exam
  - congested gray/blue turbinates
  - nasal tip transverse crease
  - reversible obstruction with topic decongestant
- allergy testing

Treatment
- allergen identification and avoidance
- nasal saline irrigation
- oral antihistamine (e.g. desloratadine, fexofenadine, loratadine, cetirizine)
- intranasal corticosteroid (mainstay of treatment)
- combination intranasal corticosteroid/antihistamine spray
- leukotriene receptor antagonist
- allergen immunotherapy
- other therapies: decongestants (risk of rhinitis medicamentosa), oral corticosteroids, eye drops

Vasomotor Rhinitis

Definition
- rhinitis secondary to changes in vascular permeability caused by dysregulation of nociceptors and autonomic nerves

Etiology
- temperature change
- alcohol, dust, smoke
- stress, anxiety, neurosis

Clinical Features
- chronic intermittent nasal obstruction, varies from side to side
- similar to allergic rhinitis
- nasal allergy must be ruled out

Treatment
- elimination of irritant factors
- congestion-predominant:
  - intranasal antihistamine
  - INCS
  - combination INCS/antihistamine
  - ± oral decongestant (risk of rhinitis medicamentosa)
- rhinorrhea-predominant:
  - intranasal anticholinergic (e.g. ipratropium)
  - ± intranasal corticosteroid, intranasal antihistamine
- symptomatic relief with exercise (increased sympathetic tone)

Rhinosinusitis

Definition
- inflammation of the mucosal lining of the sinuses and nasal passages

Pathogenesis of Rhinosinusitis
- ostial obstruction or dysfunctional cilia permit stagnant mucous and, consequently, infection
- all sinuses drain into a common area under the middle meatus called the osteomeatal complex

Classification
- acute: <4 wk
- chronic: >12 wk

Table 13. Etiologies of Rhinosinusitis

Ostial Obstruction	Inflammation	URTI Allergy
	Mechanical	Septal deviation Turbinate hypertrophy Polyps Tumours Adenoid hypertrophy Foreign body Congenital abnormalities (e.g. cleft palate)
	Immune	GPA Lymphoma, leukemia Immunosuppressed patients (e.g. neutropenics, diabetics, HIV)
Systemic		Cystic fibrosis Immotile cilia (e.g. Kartagener's syndrome)
Direct Extension	Dental	Infection
	Trauma	Facial fractures

Acute Bacterial Rhinosinusitis

Definition
- bacterial infection of the paranasal sinuses and nasal passages lasting >7 d
- clinical diagnosis requiring ≥2 major symptoms, and at least one of the symptoms is either nasal obstruction or purulent/discoloured nasal discharge
- can confirm diagnosis with CT of paranasal sinuses and/or endoscopically

	Major Symptoms (at least 2 of PODS, 1 must be O or D)	Minor Symptoms
P	Facial **P**ain/**P**ressure/fullness	Headache
O	Nasal **O**bstruction	Halitosis
D	Purulent/discoloured nasal **D**ischarge	Fatigue
S	Hyposmia/anosmia (**S**mell)	Dental pain
		Cough
		Ear pain/fullness

Etiology
- bacteria: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis, S. aureus*, anaerobes (dental)
- children are more prone to a bacterial etiology, but viral is still more common
- the maxillary sinus is the most commonly affected sinus
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless black or pale mucosa on examination)

Acute Rhinosinusitis Complications
Consider hospitalization if any of the following are suspected:

Orbital (Chandler's classification)
- I Preseptal cellulitis
- II Orbital cellulitis
- III Subperiosteal abscess
- IV Orbital abscess
- V Cavernous sinus thrombosis

Intracranial
- Meningitis
- Abscess

Bony
- Subperiosteal frontal bone abscess ("Pott's puffy tumour")
- Osteomyelitis

Neurologic
- Superior orbital fissure syndrome (CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypoesthesia)
- Orbital apex syndrome (as above, plus neuritis, papilledema, decreased visual acuity)

Clinical Features
- sudden onset of:
  - nasal blockage/congestion and/or purulent nasal discharge/posterior nasal drip
  - ± facial pain or pressure, ± hyposmia, ± sore throat
- persistent symptoms >10 d or worsening symptoms >5 d or presence of purulence for 3-4 d with high fever (>39°C)
- speculum exam: erythematous mucosa, mucopurulent discharge, pus originating from the middle meatus
- predisposing factors: viral URTI, allergy, dental disease, anatomical defects
- differentiate from acute viral rhinosinusitis (course: <10 d, peaks by day 3)

Management
- depends on symptom severity (i.e. intensity/duration of symptoms, impact on quality of life)
- mild-moderate: INCS
  - if no response within 72 h, add antibiotics
- severe: INCS + antibiotics
- antibiotics
  - 1st line: amoxicillin x 10 d (TMP-SMX or macrolide if penicillin allergy)
- if no response to 1st line antibiotics within 72 h, switch to 2nd line
  - 2nd line: fluoroquinolones or amoxicillin-clavulanic acid
- adjuvant therapy (saline or hypochlorous acid (pediatric sinusitis) irrigation, analgesics, oral/topical decongestant) may provide symptomatic relief
- CT indicated only if complications are suspected

Systemic Corticosteroid Therapy for Acute Sinusitis
JAMA 2015 Mar;313(12):1258-1259
Clinical Question: Are oral or parenteral corticosteroids associated with improved clinical outcomes in patients with acute sinusitis compared to placebo or NSAIDs?
Conclusion: Oral corticosteroids combined with antibiotics may be associated with modest benefit for short-term relief of symptoms in adults with severe symptoms of acute sinusitis compared with antibiotics alone. Oral corticosteroids as monotherapy are not associated with improved clinical outcomes in adults with clinically diagnosed acute sinusitis.

Chronic Rhinosinusitis

Definition
- inflammation of the mucosa of paranasal sinuses and nasal passages >12 wk
- diagnosis requires ≥2 major symptoms for >12 wk and ≥1 objective finding of inflammation of the paranasal sinuses (CT/endoscopy)

	Major Symptoms (similar to acute, but less severe)	Minor Symptoms
C	Facial **C**ongestion/fullness	Halitosis
P	Facial **P**ain/Pressure/fullness	Chronic cough
O	Chronic nasal **O**bstruction	Maxillary dental pain
D	Purulent anterior/posterior nasal **D**ischarge	
S	Hyposmia/anosmia (**S** mell)	

Etiology
- unclear etiology but the following may contribute or predispose
  - inadequate treatment of acute rhinosinusitis
  - untreated dental disease
  - anatomic factors (lost ostium patency, deviated septum)
  - local physiologic factors
    - ciliary disorder (e.g. cystic fibrosis, Kartagener syndrome, primary ciliary dyskinesia)
    - bacterial colonization/biofilms (*S. aureus, Enterobacteriaceae* spp., *Pseudomonas* spp., *S. pneumoniae*, group A β-hemolytic *Streptococcus*)
    - fungal infection (e.g. *Aspergillus, Zygomycetes, Candida*)
  - systemic physiologic factors
    - allergy/allergic rhinitis
    - chronic inflammatory disorder (e.g. GPA)

Allergic Fungal Rhinosinusitis
A chronic sinusitis affecting mostly young, immunocompetent, atopic individuals
Treatment options include functional ESS ± intranasal topical steroids and immunotherapy

Management
- identify and address contributing or predisposing factors
- obtain CT or perform endoscopy
- if polyps present: INCS, oral steroids ± antibiotics (if signs of infection), refer to otolaryngologist/H&N surgeon
- if polyps absent: INCS, antibiotics, saline irrigation, oral steroids (severe cases)
- antibiotics for 3-6 wk
  - amoxicillin-clavulanic acid, fluoroquinolone (moxifloxacin), macrolide (clarithromycin), clindamycin, metronidazole
- surgery if medical therapy fails or fungal sinusitis: ESS, balloon sinuplasty

ESS = Endoscopic Sinus Surgery
Opening of the paranasal sinuses in order to facilitate drainage while sparing the sinus mucosa

Complications
- same as acute sinusitis, mucocoele

Epistaxis

Blood Supply to the Nasal Septum (see *Figure 4, OT3*)

1. superior posterior septum
   - internal carotid → ophthalmic → anterior/posterior ethmoidal
2. posterior septum
   - external carotid → internal maxillary → sphenopalatine
3. lower anterior septum
   - external carotid → facial artery → superior labial artery → nasal branch
   - external carotid → internal maxillary → descending palatine → greater palatine

- vessels anastomose to form Kiesselbach's plexus, located in Little's area (anterior-inferior portion of the cartilaginous septum)

90% of nosebleeds occur in Little's area

Special Cases

Adolescent male with unilateral recurrent epistaxis: consider juvenile nasopharyngeal angiofibroma (JNA); this is the most common benign tumour of the nasopharynx

Thrombocytopenic patients: use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

Table 14. Etiology of Epistaxis

Type	Causes	
Primary Epistaxis	Idiopathic or spontaneous	
Secondary Epistaxis		
Local	Trauma (most common) Fractures: facial, nasal Self-induced: digital, foreign body	Tumours Benign: polyps, inverting papilloma, angiofibroma Malignant: SCC, esthesioneuroblastoma (olfactory neuroblastoma)
	Iatrogenic: nasal, sinus, orbit surgery	Inflammation Rhinitis: allergic, non-allergic Infections: bacterial, viral, fungal
	Nasal dryness: dry air, supplemental nasal oxygen	
	Structural abnormalities: septal deviation, chronic septal perforation	
	Chemical: nasal cocaine, nasal sprays, etc.	
Systemic	Coagulopathies Medications: anticoagulants, NSAIDs Hemophilias, von Willebrand disease Hematological malignancies Liver failure, uremia	
	Vascular: HTN, atherosclerosis, Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia)	
	Others: GPA, SLE	

Investigations

- CBC, PT/PTT/INR/platelet function assay (if suspicious of bleeding disorder)
- CT as needed

Treatment

- locate bleeding and achieve hemostasis

1. ABCs

- lean patient forward to minimize swallowing blood and avoid airway obstruction
- apply constant firm pressure for 15 to 20 min on cartilaginous part of nose (not bony pyramid) while the head is in neutral position
- if significant bleeding, assess vitals for signs of hemorrhagic shock ± IV NS, cross-match blood

2. Determine Site of Bleeding

- anterior/posterior hemorrhage defined by location in relationship to bony septum
- visualize nasal cavity with speculum
- use cotton pledget with topical lidocaine ± topical decongestant (Otrivin®) to help identify area of bleeding (often anterior septum)

3. Control the Bleeding

- first-line: topical decongestant (Otrivin®)
- if first-line fails and bleeding source adequately visualized, cauterize with silver nitrate
- **do not cauterize both sides of the septum** at one time due to risk of septal perforation from loss of septal blood supply

A. Anterior hemorrhage treatment

- if failure to achieve hemostasis with cauterization
  - place anterior pack with expandable nasal tampons (Merocel®) or fabric sponges (Rapid Rhino Riemann)*
  - consider lubricated absorbable packing (e.g. Gelfoam wrapped in Surgicel®) for patients with coagulopathy or on anticoagulation medication to prevent recurrent epistaxis from packing removal
  - alternatively, use a half inch Vaseline®-soaked ribbon gauze strips layered from nasal floor toward nasal roof and extending to posterior choanae
  - can also apply Floseal® (hemostatic matrix consisting of topical human thrombin and cross-linked gelatin) if other methods fail

B. Posterior hemorrhage treatment
- if unable to visualize bleeding source, the source is likely posterior
  - place posterior pack* using a Foley catheter, gauze pack, or Epistat® balloon
  - subsequently, layer anterior packing bilaterally
  - admit to hospital with packs in for 3 d
  - watch for complications: hypoxemia (nasopulmonary reflex), toxic shock syndrome (remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration

C. If anterior/posterior packs fail to control epistaxis
- transnasal endoscopic sphenopalatine artery ligation ± anterior ethmoid artery ligation by otolaryngology or embolization of culprit arterial supply by interventional radiology
- ± septoplasty

*antibiotics for any posterior pack or any pack left for >48 h due to risk of toxic shock syndrome

4. Prevention
- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of HTN and coagulopathies

Hoarseness

Definitions
- change in voice quality, ranging from voice harshness to voice weakness
- reflects abnormalities anywhere along the vocal tract from oral cavity to the lungs
- dysphonia: a general alteration in voice quality
- aphonia: no sound emanates from vocal folds

If hoarseness is present for >2 wk in a smoker, laryngoscopy must be done to rule out malignancy

Acute Laryngitis

Definition
- <2 wk inflammatory changes in laryngeal mucosa after exposure to a trigger

Etiology
- infectious (most common): viral (influenza, adenovirus, HSV), bacterial (Group A *Streptococcus*), fungal
- mechanical: acute voice strain → submucosal hemorrhage → vocal cord edema → hoarseness
- environmental: toxic fume inhalation

Clinical Features
- URTI symptoms, hoarseness, aphonia, cough attacks
- true vocal cords erythematous/edematous with vascular injection and normal mobility

Treatment
- usually self-limited, resolves within 1-2 wk
- voice rest
- humidification
- hydration
- avoid irritants (e.g. smoking, caffeine)
- treat with antibiotics if there is evidence of coexistent bacterial pharyngitis
- treat with proton pump inhibitors if there is evidence of reflux

Vocal Cord Paralysis
Unilateral: Affected cord lies in the paramedian position, inadequate glottic closure during phonation → weak, breathy voice. Usually medializes with time, whereby phonation and aspiration improve. Treatment options include voice therapy, injection laryngoplasty (Radiesse), medialization using silastic block, recurrent laryngeal nerve reinnervation (recurrent laryngeal nerve anastomosis to ansa cervicalis)
Bilateral: Cords rest in midline, therefore voice remains unchanged but respiratory function is compromised and may present as stridor. If there are no respiratory issues, monitor closely and wait for improvement. If respiratory issues, try CPAP or intubate if necessary. The patient will likely require vocal cord lateralization, arytenoidectomy, posterior costal cartilage graft, or tracheotomy. Selective nerve reinnervation (Marie Technique) in the proper hands may reestablish movement

Chronic Laryngitis

Definition
- >3 wk inflammatory changes in laryngeal mucosa

Etiology
- repeated attacks of acute laryngitis
- infectious: chronic rhinosinusitis with postnasal drip
- mechanical: chronic voice strain
- environmental: chronic irritants (dust, smoke, chemical fumes), chronic alcohol use
- esophageal disorders: GERD, Zenker's diverticulum, hiatus hernia
- systemic: allergy, hypothyroidism, Addison's disease

Clinical Features
- chronic dysphonia
- cough, globus sensation, frequent throat clearing 2° to GERD
- laryngoscopy: erythematous and thickened cords with ulceration/granuloma formation and normal mobility, rule out malignancy

Treatment
- remove offending irritants
- treat related disorders (e.g. antisecretory therapy for GERD)
- speech therapy with vocal rest
- ± antibiotics ± steroids to decrease inflammation

Vocal Cord Polyps

Definition
- structural manifestation of vocal cord irritation
- acutely, polyp forms 2° to capillary damage in the subepithelial space during extreme voice exertion

Etiology
- most common benign tumour of vocal cords
- voice strain (e.g. muscle tension dysphonia)
- laryngeal irritants (e.g. GERD, allergies, tobacco)

Epidemiology
- ages 30-50 y/o
- M>F

Clinical Features
- primary symptom is dysphonia ± dyspnea (if polyps are large)
- other symptoms: hoarseness, aphonia, cough attacks
- pedicled or sessile polyp on free edge of vocal cord
- typically, polyp is asymmetrical, soft, and smooth
- more common on the anterior 1/3 of the vocal cord

Treatment
- avoid irritants
- voice therapy may improve voice
- vocal fold steroid injections (percutaneous or transoral)
- endoscopic laryngeal microsurgical removal if persistent or if high-risk of malignancy

Vocal Cord Nodules

Definition
- vocal cord callus, bilateral by definition and symmetric
- also known as "screamer's" or "singer's" nodules

Etiology
- early nodules occur secondary to submucosal hemorrhage
- mature nodules result from hyalinization, which occurs with long-term voice abuse
- chronic voice strain
- frequent URTI, smoking, alcohol consumption

Epidemiology
- frequently in singers, children, bartenders, and school teachers
- F>M

Clinical Features
- hoarseness worst at end of day
- on laryngoscopy
  - bilateral symmetric nodules at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords (point of maximal cord vibration)
- chronic nodules may become fibrotic, hard, and white

Treatment
- primary treatment is voice rest and voice therapy
- hydration
- avoid irritants
- surgery rarely indicated for refractory nodules

Vocal Cords: Polyps vs. Nodules

Polyps	Nodules
Unilateral, asymmetric	Bilateral
Acute onset	Gradual onset
May resolve spontaneously	Often follow a chronic course
Subepithelial capillary breakage	Acute: submucosal hemorrhage or edema
Soft, smooth, fusiform, pedunculated mass	Acute: small, discrete nodules Chronic: hard, white, thickened, fibrosed nodules
Proton pump inhibitor	Vocal rest with whispering, hydration, voice therapy
Surgical excision if persistent or in the presence of risk factors for laryngeal cancer	Surgical excision as last resort

Recurrent Respiratory Papillomatosis

Definition
- small, benign wart-like growths (papillomas) in the respiratory tract

Etiology
- most commonly HPV types 6, 11, but can be caused by types 16, 18, 31, 33
- possible hormonal influence, possibly acquired during delivery through birth canal

Epidemiology
- biphasic distribution
  - birth to puberty (most common laryngeal tumour)
  - adult-onset (age >12 y)

Clinical Features
- progressive hoarseness, stridor, and respiratory distress; less commonly wheezing, chronic cough, recurrent pneumonia, dyspnea, hemoptysis, dysphagia, failure to thrive, apneic events
- can seed into tracheobronchial tree
- highly resistant to complete removal, high tendency of recurrence
- some juvenile papillomas resolve spontaneously at puberty
- may undergo malignant transformation to squamous cell carcinoma

Investigations
- flexible nasolaryngoscopy shows wart-like lesions with vascular core in supraglottic larynx and trachea
- bronchoscopy with biopsy to confirm diagnosis and rule out malignancy
- chest x-ray followed by CT chest if indicated. Findings of pulmonary involvement require referral to respirology
- for high-risk patients, rule out TB, HIV

Treatment
- prevention using quadrivalent HPV recombinant vaccine
- suspension microlaryngoscopy with laser removal and preservation of normal mucosa is gold standard (not curative, goal is improvement in voice and/or breathing)
  - preferably with CO_2 or KTP laser
  - other options include microdebridement and cold steel
- consider systemic adjuvants if requiring >4 surgeries/yr. These include quadrivalent HPV recombinant vaccine, bevacizumab, cidofovir, interferon, indole-3-carbinol
- PPI if concomitant GERD

Laryngeal Carcinoma

- see *Neoplasms of the Head and Neck, OT35*

Salivary Glands

Sialadenitis

Definition
- inflammation of salivary glands

Etiology
- viral most common (mumps)
- bacterial causes: *S. aureus, S. pneumoniae, H. influenzae*
- obstructive vs. non-obstructive
  - obstructive infection involves salivary stasis and retrograde bacterial flow

Predisposing Factors
- HIV
- anorexia/bulimia
- Sjögren's syndrome
- Cushing's syndrome, hypothyroidism, DM
- hepatic/renal failure
- medications that increase stasis: diuretics, tricyclic antidepressants, β-blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)

Bilateral enlargement of the parotid glands may be a manifestation of a systemic disease, such as mumps, HIV, Sjögren's, or an eating disorder (i.e. anorexia, bulimia)

Mumps usually presents with bilateral parotid enlargement ± SNHL ± orchitis

Treatment of Sialadenitis (MASH) Mnemonic

Massage
Analgesics/Antibiotics
Sialogogues
Heat/Hydration

Clinical Features
- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- ± fever
- ± leukocytosis
- ± suppurative drainage from punctum of the gland

Investigations
- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

Treatment
- hydration, warm compresses, sialogogues, massage
- if bacterial: cloxacillin ± abscess drainage

Sialolithiasis

Definition
- ductal stone (mainly hydroxyapatite in adults, sand/sludge in children), leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

Risk Factors
- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, diabetes, EtOH, hypercalcemia, psychiatric medications)

Clinical Features
- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculus

Investigations
- U/S first, and if stone identified, CT for localization; may consider sialogram

Treatment
- may resolve spontaneously
- encourage salivation to clear calculus
- massage, bimanual expression, analgesia, antibiotics, sialogogues (e.g. lemon wedges, sour lemon candies), warm compresses
- remove calculi endoscopically, by dilating duct or orifice, or by excision through floor of the mouth
- gland-preserving surgery has long-term symptom improvement and favourable gland retention rates

Salivary Gland Neoplasms

Etiology
- anatomic distribution
  - parotid gland: 70-85%
  - submandibular gland: 8-15%
  - sublingual gland: 1%
  - minor salivary glands: 5-8%
- malignant (see *Table 16, OT36* and *Table 17, OT37*)
- benign
  - benign mixed (pleomorphic adenoma): 80%
  - Warthin's tumour (5-10% bilateral, M>F): 10%
  - cysts, lymph nodes, and adenomas: 10%
  - oncocytoma: <1%

Parotid Gland Neoplasms

A mass sitting above an imaginary line drawn between the mastoid process and angle of the mandible is a parotid neoplasm until proven otherwise

Clinical Features
- 80% benign (most common: pleomorphic adenoma), 20% malignant (most common: mucoepidermoid)
- if bilateral, suggests benign process (e.g. Warthin's tumour, Sjögren's, bulimia, mumps) or possible lymphoma
- facial nerve involvement (e.g. facial paralysis) increases risk of malignancy

Investigations
- FNA biopsy
- CT, U/S, or MRI to determine extent of tumour

Treatment
- treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
- pleomorphic adenomas are excised due to risk of malignant transformation (5% risk over prolonged period of time)
- superficial tumour
  - superficial parotidectomy above plane of CN VII ± radiation
  - incisional biopsy contraindicated
- deep lesion
  - near-total parotidectomy sparing as much of CN VII as possible
  - if CN VII involved, then it is removed and cable grafted
- complications of parotid surgery
  - hematoma, infection, salivary fistula, temporary or permanent facial paresis, Frey's syndrome (gustatory sweating), sialocele, numbness of the overlying skin
- postoperative radiotherapy, if high risk of locoregional recurrence
- chemotherapy is largely reserved for palliative cases

Prognosis
- benign: excellent, <5% of pleomorphic adenomas recur
- malignant: dependent on stage and type of malignancy (see *Table 17, OT37*)

DDx Parotid Tumour

Benign
- Pleomorphic adenoma
- Warthin's tumour (M>F)
- Benign lymphoepithelial cysts (viral etiology, e.g. HIV)
- Oncocytoma

Malignant
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma

Frey's syndrome is a postoperative complication characterized by gustatory sweating. It is thought that damaged parasympathetic nerve fibres of the auriculotemporal nerve regenerates abnormally to innervate the cutaneous sweat glands

Neck Masses

Approach to a Neck Mass

- ensure that the neck mass is not a normal neck structure (e.g. hyoid, transverse process of C1 vertebra, prominent carotid bulb)
- any neck mass persisting for >2 wk should be investigated for possible neoplastic causes

Table 15. Prevalence of Acquired Causes of Neck Lumps According to Age

Age (yr)	Possible Causes of Neck Lump		
<40	1. Inflammatory	2. Congenital/Developmental	3. Neoplastic
>40	1. Neoplastic	2. Inflammatory	3. Congenital

Differential Diagnosis
- congenital
  - lateral (branchial cleft cyst, laryngocele, plunging ranula, lymphatic/venous/venolymphatic malformation)
  - midline (thyroglossal duct cyst, dermoid cyst, teratoma, thyroid/thymus anomaly, vascular malformation)
- infectious/inflammatory
  - reactive lymphadenopathy (2° to tonsillitis, pharyngitis)
  - infectious mononucleosis
  - Kawasaki, Kikuchi-Fujimoto, Kimura, Cat-scratch, Castleman, Rosai-Dorfman disease
  - HIV
  - sialolithiasis, sialadenitis
  - thyroiditis
- granulomatous disease
  - mycobacterial infections
  - sarcoidosis
- neoplastic
  - lymphoma
  - salivary gland tumours
  - thyroid tumours
  - metastatic malignancy ("unknown primary")
  - lipoma, fibroma, hemangioma, nerve or nerve sheath tumour

Evaluation

Investigations

- history and physical (including nasopharynx and larynx)
- all other investigations and imaging are dependent upon clinical suspicion following history and physical
  - congenital: CT with contrast, excisional biopsy
  - inflammatory/infectious: WBC (infection vs. lymphoma), trial of antibiotics, chest radiograph, Mantoux TB test, CT with contrast, FNA
  - neoplasms: thyroid function tests and scans, CT with contrast, FNA (histologic examination), panendoscopy (identification of possible primary tumour)
    - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
    - primary identified 95% of time → stage and treat
    - primary occult identified 5% of time: excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (SCC)

Inflammatory vs. Malignant Neck Masses

	Inflammatory	Neoplastic
History		
Painful	Y	Y/N
H&N infection	Y	N
Fever	Y	N
Weight loss	N	Y
CA risk factors	N	Y
Age	Younger	Older
Physical		
Tender	Y	N
Rubbery	Y	N
Rock hard	N	Y
Mobile	Y	± fixed

Congenital Neck Masses

Branchial Cleft Cysts/Sinuses/Fistulae

Embryology

- at 4th wk of embryonic development, there are 4 pairs of branchial arches and 2 rudimentary arches, which are separated internally by pouches and externally by clefts
- branchial anomalies form when pouches and clefts persist and fall into 3 types:
  1. branchial fistula: persistent communication between skin and GI tract
  2. branchial sinus: blind-ended tract opening to skin
  3. branchial cyst: persistent cervical sinus with no external opening

Clinical Features

- 2nd branchial cleft malformations most common
  - sinuses and fistulae present in infancy as a small opening anterior to the SCM muscle
  - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following a URTI
- 1st branchial cleft malformations present as sinus/fistula or cyst in preauricular area (Type I) or on face over angle of mandible (Type II)
- 3rd branchial cleft malformations present as recurrent thyroiditis or thyroid abscess and have a tract which usually leads to the left pyriform sinus. Air on CT scan in or near the thyroid gland is pathognomonic for this anomaly
- there is controversy whether 4th branchial cleft anomalies exist, as they may be remnants of the thyrothymic axis

Treatment

- surgical removal of cyst or fistula tract
- if infected: allow infection to settle before removal (antibiotics may be required)

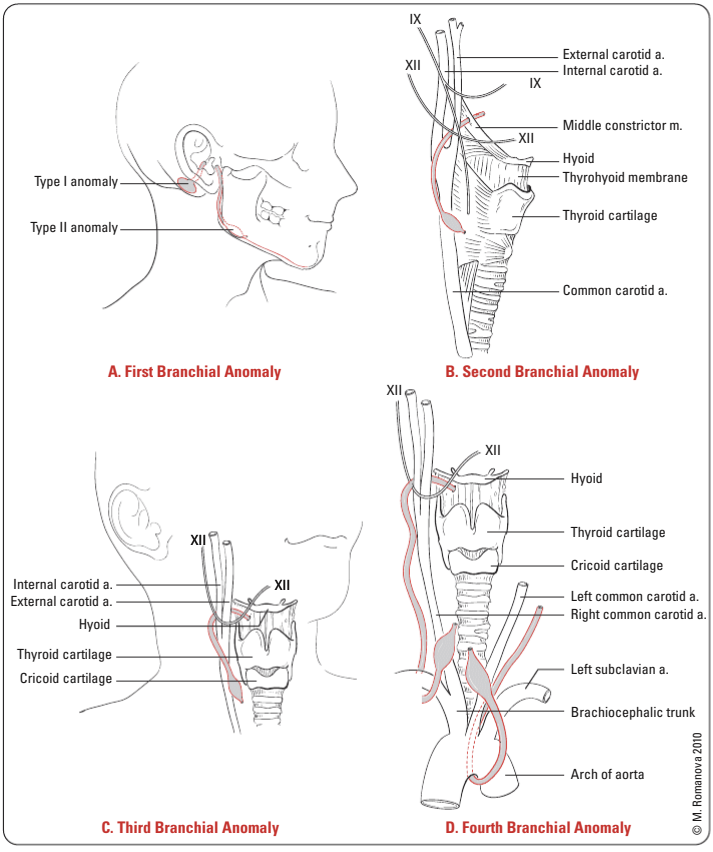


Figure 19. Branchial cleft anomalies

Thyroglossal Duct Cysts

Embryology

- vestigial remnant of tract made by thyroid gland as it travels from its origin as a ventral midline diverticulum at the base of the tongue, caudal to the junction of 3rd and 4th branchial arches (foramen cecum), and migrates to the inferior aspect of the neck (see *Figure 19*)

Clinical Features

- most common congenital cervical anomaly
- usually presents in childhood or from ages 20-40 as a midline cyst that enlarges with URTI and elevates with swallowing and tongue protrusion
- location can be suprahyoid or infrahyoid
- may have fibrous cord, dysphagia, globus sensation

Thyroglossal duct cysts are the most common congenital neck mass found in children

Treatment

- preoperative antibiotics to reduce inflammation (infection before surgery is a well-described cause of recurrence)
- small potential for neoplastic transformation, so complete excision of cyst and tissue around tract up to foramen cecum at base of tongue, with removal of central portion of hyoid bone (Sistrunk procedure) recommended

Lymphatic, Venous, or Mixed Venolymphatic Malformations

Definition
- lymphatic malformation arising from vestigial lymph channels of neck

Clinical Features
- commonly identified in many fetuses, but regress before birth and never cause a clinical problem
- usually present by age 2
- macrocystic: soft, painless compressible mass (lymphatic dilation) with skin discolouration
- microcystic: soft, noncompressible masses with mucosal or skin vesicles
- may have dysphagia, dyspnea, possible pain with acute infection
- infection or trauma causes a sudden increase in size

Treatment
- can regress spontaneously after bacterial infection, therefore do not plan surgical intervention until several mo after infection
- macrocystic lesions can be treated by surgical excision or sclerotherapy (doxycycline)
- microcystic lesions are difficult to treat, but can be debulked if it will not cause loss of function of normal structures, or injected with sclerotherapy (bleomycin) in surrounding tissues

Neoplasms of the Head and Neck

Pre-Malignant Disease
- lichen planus
  - lacy white lines of oral mucosa ± erythema
  - exact cause unknown, thought to be immune-mediated
  - treatment: topical corticosteroids (first-line), topical calcineurin inhibitors (second-line)
  - risk of malignant transformation 5-10%, follow-up every 6-12 mo
- leukoplakia
  - white keratotic plaque/patch of oral mucosa that cannot be rubbed off
  - treatment: surgery, cryosurgery, laser ablation, retinoids
  - risk of malignant transformation 5-20%, follow-up every 3-12 mo
- erythroplakia
  - red mucosal plaque adjacent to normal mucosa
  - commonly associated with epithelial dysplasia
  - associated with carcinoma *in situ* or invasive tumour in 40% of cases
  - treatment: similar to leukoplakia
- dysplasia (a feature of pre-malignant lesions)
  - histopathologic presence of mitoses and prominent nucleoli
  - involvement of entire mucosal thickness = carcinoma *in situ*
  - associated progression to invasive cancer 15-30%

Investigations
- initial metastatic screen includes chest x-ray
- scans of liver, brain, and bone only if clinically indicated
- CT scan superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI superior for discriminating tumour from mucus and detecting bone marrow invasion
- ± PET scans
- endoscopy with biopsy

Treatment
- treatment depends on:
  - histologic grade and stage of tumour
  - physical and psychological health of patient
  - facilities available, expertise and experience of the medical and surgical oncology teamteam
- in general:
  - 1° surgery for malignant oral cavity tumours with radiotherapy reserved for salvage or poor prognostic indicators
  - 1° radiotherapy for nasopharynx, oropharynx, hypopharynx, and larynx malignancies with surgery reserved for salvage, although laser endoscopic surgery for early stage larynx cancer is an option and 1° surgery for advanced (T4) pharyngeal and laryngeal cancer is the standard of care
  - there is a growing interesting in studying 1° surgery (transoral surgery) for OPC
  - palliative chemotherapy for metastatic or incurable disease
  - concomitant chemotherapy increases survival in advanced disease
  - chemotherapy has a role as induction therapy prior to surgery and radiation
  - panendoscopy (bronchoscopy, esophagoscopy, laryngoscopy, and pharyngoscopy) to detect 1° disease when lymph node metastasis is identified
  - anti-epidermal growth factor receptor treatment (cetuximab, panitumumab) has a role as concurrent therapy with radiation for SCC of the H&N (for advanced local and regional disease)

All patients presenting with a H&N mass should be asked if they are experiencing the following obstructive, referred, or local symptoms
Oropharyngeal: Odynophagia, dysphagia, non-healing oral ulcers
Otologic: Otalgia, HL
Laryngeal: Dyspnea or stridor (positional vs. non-positional), hoarseness, dysphonia → positional vs. non-positional
Nasopharyngeal: Recurrent epistaxis, unilateral nasal obstruction, persistent rhinorrhea or sinusitis
Hemoptysis, hematemesis

Detection of cervical lymph nodes on physical exam
False negative rate: 15-30%
False positive rate: 30-40%

Pathological lymphadenopathy defined radiographically as
A jugulodigastric node >1.5 cm in diameter, or a retropharyngeal node >1 cm in diameter
A node of any size which contains central necrosis

Common sites of distant metastases for H&N neoplasms
(most common to least common) lungs > liver > bones

Risk Factors for H&N Cancer
- Smoking
- EtOH (synergistic with smoking)
- Radiation
- Occupational/environmental exposures
- Oral HPV infection (independent of smoking and EtOH exposure)
- Family history of cancer
- Previous cancer

The smaller the salivary gland, the greater the likelihood that a mass in the gland is malignant

Prognosis

- synchronous tumours occur in 0.8-18% of patients
- late development of second primary is most common cause of post-treatment failure after 36 mo

Table 16. Quick Look-Up Summary of H&N Malignancies – Etiology and Epidemiology

Etiology	Epidemiology	Risk Factors
Oral Cavity		
95% SCC Others: sarcoma, melanoma, minor salivary gland tumour	Mean age: 50-60 yr M>F Most common site of H&N cancers 50% on anterior 2/3 of tongue	Smoking/EtOH Poor oral hygiene Leukoplakia, erythroplakia Lichen planus, chronic inflammation Sun exposure – lip HPV infection Plummer-Vinson syndrome Genetic/Ethnic
Nose and Paranasal Sinus		
75-80% SCC Adenocarcinoma (2nd most common) and mucoepidermoid 99% in maxillary/ethmoid sinus 10% of nose and paranasal sinus tumours arise from minor salivary glands	Mean age: 50-70 yr Rare tumours ↓ incidence in last 5-10 yr	Wood/shoe/textile industry Hardwood dust (nasal/ethmoid sinus) Nickel, chromium (maxillary sinus) Air pollution Chronic rhinosinusitis
Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx, and Larynx)		
Nasopharynx		
90% SCC ~10% lymphoma	Mean age: 50-59 yr M:F=2.4:1 Incidence 0.8 per 100000 100x increased incidence in Southern Chinese	EBV Salted fish Nickel exposure Poor oral hygiene Genetic – Southern Chinese
Oropharynx		
95% SCC – poorly differentiated Up to 70% of OPC attributable to HPV	Mean age: 50-70 yr HPV+ patients with OPC are approximately 10 yr younger Prevalence of HPV+ OPC has increased by 225% from 1988 to 2004 M:F=4:1	Smoking/EtOH HPV 16 infection
Hypopharynx		
95% SCC 3 sites 1. pyriform sinus (60%) 2. postcricoid (30%) 3. posterior pharyngeal wall (10%)	Mean age: 50-70 yr M>F 8-10% of all H&N cancer	Smoking/EtOH
Larynx		
SCC most common 3 sites 1. supraglottic (30-35%) 2. glottic (60-65%) 3. subglottic (1%)	Mean age: 45-75 yr M:F=10:1 45% of all H&N cancer	Smoking/EtOH
Salivary Gland		
40% mucoepidermoid 30% adenoid cystic 5% acinic cell 5% malignant mixed 5% lymphoma	Mean age: 55-65 yr M=F 3-6% of all H&N cancer Percentage of malignant tumours in each gland: Parotid 15-25% Submandibular 37-43% Minor salivary >80%	Radiation exposure
Thyroid (90% benign – 10% malignant)		
>80% papillary 5-15% follicular 5% medullary <5% anaplastic 1-5% Hürthle cell 1-2% metastatic	Children Adults <30 or >60 yr Nodules more common in females Malignancy more common in males	Radiation exposure Family history – papillary CA or multiple endocrine neoplasia (MEN II) Older age Male Papillary – Gardner's syndrome, Cowden syndrome, FAP

HPV and Survival of Patients with OPC
NEJM 2010;363(1):24-35
Methods: Retrospective analysis of patients with stage III or IV oropharyngeal SCC enrolled in a RCT comparing accelerated or standard fractionation radiotherapy, each combined with cisplatin therapy.
Results: Similar 3 yr overall survival rates in both treatment arms. Patients with HPV-positive tumour had better rates of overall survival at 3 yr (82.4% vs. 57.1%) and a 58% reduction in risk of death (Hazard Ratio: 0.42, 95% CI 0.27-0.66) after adjusting for age, race, tumour and nodal stage, tobacco exposure, and treatment.
Summary: The tumour HPV status of patients with oropharyngeal SCC is a strong and independent prognostic factor for survival.

Summary of Treatment for Head and Neck Masses
Stage I/II: single modality
Stage III/IV: dual modality

Table 17. Quick Look-Up Summary of H&N Malignancies – Diagnosis and Treatment

Clinical Features	Investigations	Treatment	Prognosis
Oral Cavity			
Asymptomatic neck mass (30%) Non-healing ulcer ± bleeding Dysphagia, sialorrhea, dysphonia Oral fetor, otalgia, leukoplakia, or erythroplakia (pre-malignant changes or clinically isolated syndrome)	Biopsy CT	1º surgery local resection ± neck dissection ± reconstruction 2º radiation	5 yr overall survival T1/T2: 75% T3/T4: 30-35% Poor prognostic indicators Depth of invasion, close surgical margins location (tongue worse than floor of mouth) Cervical nodes
Nose and Paranasal Sinus			
Early Symptoms Unilateral nasal obstruction Epistaxis, rhinorrhea	CT/MRI Biopsy	Surgery and radiation Chemoradiotherapy	5 yr survival: 30-60% Poor prognosis secondary to late presentation
Late Symptoms 2º to invasion of nose, orbit, nerves, oral cavity, skin, skull base, cribriform plate			
Nasopharynx			
Cervical nodes (60-90%) Nasal obstruction, epistaxis Unilateral otitis media ± HL CN III to VI, IX to XII (25%) Proptosis, voice change, dysphagia	Nasopharyngoscopy Biopsy CT/MRI	1º radiation ± chemoradiation Surgery for limited or recurrent disease	5 yr survival T1: 79% T2: 72% T3: 50-60% T4: 36-42%
Oropharynx			
Odynophagia, otalgia Ulcerated/enlarged tonsil Fixed tongue/trismus/dysarthria Oral fetor, bloody sputum HPV+ OPC predominantly arises at base of tongue or tonsillar region Cervical lymphadenopathy (60%) Distant mets: lung/bone/liver (7%)	Biopsy Determine HPV status via RT-PCR: positive if presence of HPV DNA and p16 overexpression CT	1º radiation, consider therapy de-intensification for HPV+ patients 2º surgery local resection ±neck dissection ±reconstruction 1º surgery emerging role of Transoral Robotic Surgery	5 yr overall survival Stratified by TNM stage (I, II, III, IV) HPV negative OPC (70%, 58%, 50%, 30%) HPV positive OPC (92%, 87%, 74%, 40%) HPV positive OPC further stratified by stage, age, and smoking pack years (PY) group I (T1-3N0-N2c, ≤20 PY): 89% group II (T1-3N0-N2c, >20 PY): 64% group III (T4 or N3, age ≤70): 57% group IVA (T4 or N3, age >70): 40%
Hypopharynx			
Dysphagia, odynophagia Otalgia, hoarseness Cervical lymphadenopathy	Pharyngoscopy Biopsy CT	1º radiation 2º surgery	5 yr survival T1: 53% T2/T3: 36-39% T4: 24%
Larynx			
Dysphagia, odynophagia, globus Otalgia, hoarseness Dyspnea/stridor Cough/hemoptysis Cervical nodes (rare with glottic CA)	Laryngoscopy Biopsy CT/MRI	Early stage: single modality (radiation or surgery) Late stage: multimodality (surgery, radiotherapy, chemotherapy)	5 yr survival T4: >40% (surgery with radiation) Control rate early lesions: >90% (radiation) 10 to 12% of small lesions fail radiotherapy
Salivary Gland			
Painless mass (occ. pain is possible) CN VII palsy Cervical lymphadenopathy Rapid growth Invasion of skin Constitutional signs/symptoms	FNA MRI/CT/U/S	1º surgery ± neck dissection Postoperative radiotherapy Chemotherapy if unresectable	Parotid 10 yr survival: 85%, 69%, 43%, and 14% for stages T1 to T4 Submandibular 2 yr survival: 82%, 5 yr: 69% Minor salivary gland 10 yr survival: 83%, 52%, 25%, and 23% for stages T1 to T4
Thyroid			
Thyroid mass, cervical nodes Vocal cord paralysis, hoarseness Hyper/hypothyroidism Dysphagia	FNA U/S	1º surgery $I^{131}$for intermediate and high-risk well-differentiated thyroid cancer	Recurrences occur within 5 yr Need long-term follow-up: clinical exam, thyroglobulin
Parathyroid			
Symptoms of hypercalcemia Neck mass Bone disease, renal disease Pancreatitis	Sestamibi	Wide surgical excision Postoperative monitoring of serum Ca^{2+}	Recurrence rates 1 yr: 27% 5 yr: 82% 10 yr: 91% Mean survival: 6-7 yr

CT imaging for Head and Neck Malignancies are done with contrast for the neck and chest. CT head is not routinely order.

Thyroid Carcinoma

Table 18. Bethesda Classification of Thyroid Cytology

Diagnostic Category	Risk of Malignancy
Non-diagnostic or unsatisfactory	1-4%
Benign	0-3%
Follicular lesion of undetermined significance or atypia of undetermined significance	5-15%
Follicular neoplasm or suspicious for a follicular neoplasm	15-30%
Suspicious for malignancy	60-75%
Malignant	97-99%

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a reporting system for thyroid FNA.

Table 19. Thyroid Carcinoma

	Papillary	Follicular	Medullary	Anaplastic	Lymphoma
Incidence (% of all thyroid cancers)	90-92%	4-6%	1-2%	<1%	<1% Most common is diffuse large B-cell lymphoma
Route of Spread	Lymphatic	Hematogenous		N/A	
Histology	Orphan Annie nuclei Psammoma bodies Papillary architecture	Capsular/vascular invasion influences prognosis	Amyloid May secrete calcitonin, prostaglandins, ACTH, serotonin, kallikrein, or bradykinin	Giant cells Spindle cells	
Other	**P**s – **P**apillary cancer **P**opular (most common) **P**alpable lymph nodes **P**ositive I^{131} uptake **P**ositive prognosis **P**ostoperative I^{131} scan to guide treatments	**F**s – **F**ollicular cancer **F**ar away mets **F**emale (3:1) **N**OT FNA (cannot be diagnosed by FNA) **F**avourable prognosis	**M**s – **M**edullary cancer **M**ultiple endocrine neoplasia (**MEN** IIa or IIb) a**M**yloid **M**edian node dissection	More common in elderly 70% in women 20-30% have Hx of differentiated thyroid CA (mostly papillary) or nodular goitre mass Rapidly enlarging neck Rule out lymphoma	Usually non-Hodgkin's lymphoma Rapidly enlarging thyroid mass Hx of Hashimoto's thyroiditis Increases risk 60x 4:1 female predominance Dysphagia, dyspnea, stridor, hoarseness, neck pain, facial edema, accompanied by "B" symptoms*
Prognosis	98% at 10 yr	92% at 10 yr			5 yr survival Stage IE: 55-80% Stage IIE: 20-50% Stage IIE/IV: 15-35%
Treatment	Early stage: total or near total thyroidectomy (<4 cm, no high risk features) or total thyroidectomy (≥4 cm) Late stage: total thyroidectomy ± neck dissection ± postoperative I^{131} treatment	Early stage: total or near total thyroidectomy Late stage: total thyroidectomy ± neck dissection ± postoperative I^{131} treatment	Total thyroidectomy Median and/or lateral compartment node neck dissection (based on serum calcitonin) Modified neck dissection Postoperative thyroxine, radiotherapy Tracheostomy Screen relatives Targeted therapy for metastatic palliative cases	Tracheostomy Local tumour: total thyroidectomy Radiotherapy Chemotherapy and targeted therapy Palliative Care	Non-surgical Combined radiation Chemotherapy (CHOP**)

*B symptoms = fever, night sweats, chills, weight loss >10% in 6 mo
** CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

Approach to Thyroid Nodule

- all patients with thyroid nodules require evaluation of serum TSH and ultrasound of the thyroid gland, central and lateral neck
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule
- molecular testing is increasingly used to identify gene mutations associated with thyroid cancers to determine "high-risk" from "low-risk" thyroid nodules
- Thyroid Imaging, Reporting and Data System (TI-RADS) provides recommendation for FNA or U/S follow-up
  - TR1 (0 points): benign, no FNA
  - TR2 (2 points): not suspicious, no FNA
  - TR3 (3 points): mildly suspicious, FNA if ≥2.5 cm, follow-up if ≥1.5 cm

- TR4 (4-6 points): moderately suspicious, FNA if ≥1.5 cm, follow-up if ≥1 cm
- TR5 (>7 points): highly suspicious, FNA if ≥1 cm, follow-up if ≥ 0.5 cm

Table 20. American College of Radiology Thyroid-Imaging, Reporting and Data System (TI-RADS)

Composition (Choose 1)	Echogenicity (Choose 1)	Shape (Choose 1)	Margin (Choose 1)	Echogenic Foci (Choose all that apply)
Cystic or almost completely cystic (0 points) Spongiform (0 points) Mixed cystic and solid (1 point) Solid or almost completely solid (2 points)	Anechoic (0 points) Hyperechoic or isoechoic (1 point) Hypoechoic (2 points) Very hypoechoic (3 points)	Wider-than-tall (0 points) Taller-than-wide (3 points)	Smooth (0 points) Ill-defined (0 points) Lobulated or irregular (2 points) Extrathyroidal extension (3 points)	None or large comet-tail artifacts (0 points) Microcalcifications (1 point) Peripheral calcifications (2 points) Punctate echogenic foci (3 points)

Table 21. Management of the Thyroid Nodule

Treatment	Indications
Radioiodine therapy	Treatment of hyperthyroidism After surgery as adjuvant treatment of intermediate-high-risk papillary or follicular carcinoma
Chemotherapy and targeted therapy (tyrosine kinase inhibitors)	Recurrent/residual medullary CA, anaplastic CA, or thyroid lymphoma
Surgical excision	Nodule that is suspicious on FNA cytology Malignancy other than anaplastic CA, or thyroid lymphoma Mass that is benign on FNA but increasing in size on serial imaging and/or >3-4 cm in size Hyperthyroidism not amenable to medical therapy

Indications for Postoperative Radioactive Iodine Ablation – I[131]

Adjuvant therapy: decrease recurrent disease

Radioactive Iodine (RAI) therapy: treat persistent cancer

Pediatric Otolaryngology

Acute Otitis Media

Definition

- infection of the middle ear space with both presence of MEE/MEI and acute onset of MEE/MEI symptoms

Epidemiology

- most frequent diagnosis in sick children visiting clinicians' offices and most common reason for antibiotic administration
- peak incidence between 6-15 mo: ~85% of children have >1 episode by 3 yr
- seasonal variability: peaks in winter

Etiology

- primary defect causing AOM: Eustachian tube dysfunction/obstruction → stasis/colonization by pathogens
- bacterial: *S. pneumoniae*, non-typeable *H. influenzae, M. catarrhalis*, group A *Streptococcus, S. aureus*
- viral: RSV, influenza, parainfluenza, adenovirus, coronaviruses , rhinovirus
- commonly due to bacterial/viral co-infection

Predisposing Factors

- Eustachian tube dysfunction/obstruction
  - edematous tubal mucosa
    - URTI
    - allergic rhinitis
    - chronic rhinosinusitis
    - GERD
  - obstruction/infiltration of Eustachian tube ostium
    - tumour: nasopharyngeal carcinoma (adults)
    - adenoid hypertrophy (by maintaining a source of infection rather than obstruction)
    - barotrauma (sudden changes in air pressure)
  - inadequate tensor palati function: cleft palate (even after repair)
  - abnormal Eustachian tube
    - Down syndrome (horizontal position of Eustachian tube), Crouzon syndrome, cleft palate, and Apert syndrome
- aberrant function of:
  - cilia of Eustachian tube: Kartagener's syndrome
  - mucus-secreting cells
  - capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, cystic fibrosis

Risk Factors
- non-modifiable: young age, family history of OM, prematurity, orofacial abnormalities, immunodeficiencies, Down syndrome, genetic predisposition, and lower SES
- modifiable: lack of breastfeeding, daycare attendance, household crowding, exposure to cigarette smoke or air pollution, pacifier use, vitamin A deficiency, and cochlear implants

Protective Factors
- breastfeeding
- xylitol

Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features
- triad of otalgia, fever (especially in younger children), and CHL
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if TM perforated
- infants/toddlers
  - ear-tugging (this alone is not a good indicator of pathology)
  - HL, balance disturbances (rare)
  - irritability, poor sleeping
  - vomiting and diarrhea
  - anorexia
- otoscopy of TM
  - hyperemia
  - bulging, pus may be seen behind TM
  - loss of landmarks: handle and long process of malleus not visible

Diagnosis
- history
  - acute onset of otalgia or ear tugging in a preverbal child, otorrhea, decreased hearing
  - unexplained irritability, fever, upper respiratory symptoms, poor sleeping, anorexia, N/V, and diarrhea
- physical
  - febrile
  - MEE on otoscopy: immobile TM, acute otorrhea, loss of bony landmarks, opacification of TM, air-fluid level behind TM
  - MEI on otoscopy: bulging TM with marked discolouration (hemorrhagic, red, grey, or yellow)

Management
- supportive care and symptom management: maintain hydration, analgesic, and antipyretic (acetaminophen, ibuprofen)
- watchful waiting: in a generally healthy child >6 mo of age with unilateral, non-severe, suspected AOM
  - without MEE or with MEE but non-bulging or mildly erythematous TM
- reassess in 24-48 h if not clinically improved (or earlier if worsening): mildly ill (alert, responsive, no rigors, mild otalgia, fever <39°C, <48 h illness)
  - with MEE present AND bulging TM
- if not improved or if worsening at 24-48 h follow-up, treat with antimicrobials
- antimicrobial indications: infants <6 mo of age or in a generally healthy child >6 mo of age with suspected AOM and the following features
  - moderately or severely ill (irritable, difficulty sleeping, poor antipyretic response, severe otalgia) OR fever ≥39°C OR >48 h of symptoms
  - immunocompromised, craniofacial abnormalities
  - perforated TM with purulent drainage
- referral to otolaryngology for myringotomy and tympanostomy tubes may be warranted for recurrent AOM with effusion in at least 1 ear at the time of reassessment. Recurrent AOM is defined as:
  - ≥3 AOM episodes in 6 mo
  - ≥4 AOM episodes within 12 mo and at least 1 of these episodes in the most recent 6 mo

Treatment
- antimicrobial agents for AOM
  - 5 d course of appropriate dose antimicrobial recommended for most ≥2 yr with uncomplicated AOM; 10 d course for 6-24 mo, perforated TM, or recurrent AOM
  - 1st line treatment (no penicillin allergy)
    - high-dose amoxicillin: 80-90 mg/kg/d divided BID

Clinical Assessment of AOM in Pediatrics
JAMA 2010;304:2161-69
In assessment of AOM in pediatrics, ear pain is the most useful symptom with an LR between 3.0-7.3. Useful otoscopic signs include erythematous (LR 8.4, 95% CI 7-11), cloudy (LR 34, 95% CI 28-42), bulging (LR 51, 95% CI 36-73), and immobile tympanic membrane (LR 31, 95% CI 26-37) on pneumatic otoscopy.

Antibiotics for AOM in Children
Cochrane DB Syst Rev 2013;1:CD000219
Study: Meta-analysis of Randomized Controlled Trials (RCTs) on children (1-15 mo) with acute otitis media comparing any antibiotic regime to placebo and expectant observation.
Data Sources: Cochrane Central Register of Controlled Trials (2012 issue 10), MEDLINE (1966 to October 2012), OLDMEDLINE (1958 to 1965), EMBASE (January 1990 to November 2012), Current Contents (1966 to November 2012), CINAHL (2008 to November 2012) and LILACS (2008 to November 2012) without language restrictions.
Main Outcomes: 1) Pain at 24 h, 2-3 d, and 4-7 d; 2) Abnormal tympanometry findings; 3) TM perforation; 4) Contralateral otitis; 5) AOM recurrences; 6) Serious complications from AOM; 7) Adverse effects from antibiotics.
Results: Treatment with antibiotics had no significant impact on pain at 24 h. However, pain at 2-3 d and 4-7 d was lower in the antibiotic groups with a NNT of 20. Antibiotics had no significant effect on tympanometry findings, number of AOM recurrences, or severity of complications. Antibiotic treatment led to a significant reduction in TM perforations (NNT 33) and halved contralateral AOM (NNT 11). Adverse events (vomiting, diarrhea, or rash) occurred more often in children taking antibiotics.
Conclusion: The role of antibiotics is largely restricted to pain control at 2-7 d, but most (82%) settle without antibiotics. This can also be achieved by analgesics. However, antibiotic treatment can reduce risk of TM perforation and contralateral AOM episodes. These benefits must be weighed against risks of adverse events from antibiotics.

- 2nd line treatment
  - azithromycin: 10 mg/kg (first line for penicillin allergy)
  - clarithromycin: 15 mg/kg/d divided BID (first line for penicillin allergy)
  - cefprozil: 30 mg/kg/d divided BID
  - cefuroxime axetil: 30 mg/kg/d divided BID-TID
  - ceftriaxone: 50 mg/kg IM (or IV) x 3 doses
- if initial therapy fails (i.e. no symptomatic improvement after 2-3 d)
  - high-dose amoxicillin-clavulanate: 45-60 mg/kg/d (7:1 formulation, 400 mg/5 mL suspension) for 10 d for child weighing ≤35 kg or 500 mg tablets TID for 10 d for child weighing >35 kg

Complications
- extracranial
  - HL and speech delay (secondary to persistent MEE), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
  - mastoiditis is the most common complication of AOM
- intracranial
  - meningitis, epidural/brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, sigmoid sinus thrombophlebitis, carotid artery thrombosis, facial nerve paralysis
- other
  - postauricular abscess, Bezold's abscess

Otitis Media with Effusion

Definition
- presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology
- most common cause of paediatric HL
- not exclusively a paediatric disease
- frequently follows AOM in children
- MEE have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10% (i.e. 90% of children clear the fluid within 3 mo) – observe for 3 mo before considering myringotomy and tubes)

Risk Factors
- same as AOM

Clinical Features
- CHL ± tinnitus
  - confirm with audiogram and tympanogram (flat) (see *Figure 16B, OT10* and *Figure 17, OT11*)
- aural fullness (blocked ear)
- ± pain, low grade fever
- otoscopy of tympanic membrane
  - discolouration – amber or dull grey with "glue" ear
  - meniscus fluid level behind TM
  - air bubbles
  - retraction pockets/TM atelectasis
  - most reliable finding with pneumatic otoscopy is immobility

Treatment
- expectant: 90% resolve by 3 mo
  - watchful waiting for 3 mo from onset or 3 mo from diagnosis if onset unknown
- document HL with audiogram
- recommend **against** intranasal or systemic steroids, systemic antibiotics, antihistamines, and decongestants
- surgery: myringotomy ± ventilation tubes to equalize pressure and drain ear (tympanostomy tubes recommended) ± adenoidectomy (not recommended in <4 yr unless nasal obstruction, chronic adenoiditis; recommended in ≥4 yr)

Complications of OME
- HL, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma, especially when retraction pockets involve pars flaccida
- retraction of tympanic membrane, atelectasis, ossicular fixation

Indications for Myringotomy and Tympanostomy Tubes in Recurrent AOM and OME*
- Chronic bilateral OME and documented hearing difficulties >3 mo
- Unilateral or bilateral OME >3 mo and symptoms likely attributable to OME (e.g. balance problems, poor school performance, ear discomfort, etc.)
- At-risk children (permanent HL, speech/language delay, autism-spectrum disorder, craniofacial disorders, blindness, cleft palate, developmental delay) with unilateral or bilateral OME with type B tympanogram or persistent effusion >3 mo
- Recurrent AOM (>3 episodes in 6 mo or >4 in 12 mo) with unilateral or bilateral MEE

*Clinical practice guidelines: Tympanostomy tubes in children. Otolaryng Head Neck 2013;149:S1-S35

Effectiveness of Tympanostomy Tubes for Otitis Media: A Meta-Analysis
Pediatrics 2017;139(6):e20170125
Study: Systematic review evaluating the effectiveness of tympanostomy tubes in children with chronic OM with effusion and recurrent AOM compared to watchful waiting.
Data Sources: MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, CINAHL.
Results: Children treated with tympanostomy tubes compared with watchful waiting had a net decrease (improvement) in mean hearing threshold of 9.1 dB at 1-3 mo and 0.0 by 12-24 mo. Children with recurrent AOM may have fewer episodes after tympanostomy tube.
Conclusions: Tympanostomy tubes improve hearing at 1-3 mo compared with watchful waiting, with no evidence of benefit by 12-24 mo. More evidence is needed for recurrent AOM. The benefits of tympanostomy tubes must be weighed against a variety of associated adverse events.

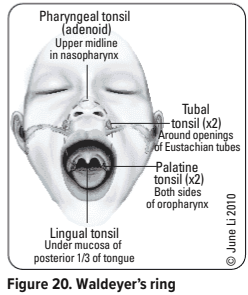


Figure 20. Waldeyer's ring
An interrupted circle of protective lymphoid tissue at the upper ends of the respiratory and alimentary tracts

Adenoid Hypertrophy

Definition
- obstructive condition due to enlarged adenoids
- increase in size with repeated URTI and allergies
- onset occurs around ages 2-4, peaks around age 5, and resolves by age 12

Clinical Features
- nasal obstruction
  - adenoid facies: open-mouthed appearance associated with high arched palate, dental crowding, hypoplastic maxilla, pinched nostrils, short upper lip, and elongated face
  - history of hypernasal voice and snoring
  - chronic mouth breathing
- choanal obstruction
  - chronic rhinosinusitis/rhinitis
  - OSA
- chronic inflammation
  - nasal discharge, post-nasal drip, and cough
  - cervical lymphadenopathy

Diagnosis
- enlarged adenoids on nasopharyngeal exam (usually with flexible nasopharyngoscope)
- enlarged adenoid shadow on lateral soft tissue x-ray (palate elevation can make adenoid look larger)

Treatment
- self-resolving due to age-related adenoid atrophy
- antibiotics, if infectious
  - uncomplicated: amoxicillin, clindamycin or azithromycin (penicillin allergies)
  - chronic or recurrent: amoxicillin-clavulanate
- adenoidectomy if recurrent/persistent obstructive or infectious symptoms

Complications
- Eustachian tube obstruction leading to serous otitis media
- interference with nasal breathing, necessitating mouth breathing
- malocclusion
- sleep apnea/respiratory disturbance
- orofacial developmental abnormalities

Adenoidectomy

Indications for Adenoidectomy
- chronic upper airway obstruction with sleep disturbance/apnea ± cor pulmonale
- chronic nasopharyngitis resistant to medical treatment
- chronic serous OM and chronic suppurative OM (with second set of tubes)
- recurrent AOM resistant to antibiotics
- suspicion of nasopharyngeal malignancy
- persistent rhinorrhea secondary to nasal obstruction
- persistent adenoiditis after two courses of antibiotics
- hyponasal speech
- dental malocclusion or orofacial growth disturbance documented by orthodontist or dentist

Contraindications
- uncontrollable coagulopathy
- recent pharyngeal infection
- conditions that predispose to velopharyngeal insufficiency (cleft palate, impaired palatal function, or enlarged pharynx)

Complications
- bleeding, infection
- velopharyngeal insufficiency (hypernasal voice or nasal regurgitation)
- scarring of Eustachian tube orifice

Sleep-Disordered Breathing in Children

Definition
- spectrum of sleep-related breathing abnormalities ranging from snoring to OSA

Epidemiology
- peak incidence between 2-8 yr when tonsils and adenoids are the largest relative to the pharyngeal airway

Etiology
- due to a combination of anatomic and neuromuscular factors
  - adenotonsillar hypertrophy
  - adenotonsillar hypertrophy
  - craniofacial abnormalities
  - neuromuscular hypotonia (e.g. cerebral palsy, Down syndrome)
  - obesity

Clinical Features
- nighttime symptoms: heavy snoring, pauses or apnea, sleeping with neck hyperextended, enuresis
- daytime symptoms: mouth breathing, excessive daytime sleepiness, behavioural/learning problems, symptoms of ADHD (e.g. inattention, hyperactivity), morning headache, failure to thrive

Investigations
- flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
- polysomnography (apnea-hypopnea index >1/h considered abnormal)
  - children: mild OSA 1-4/h; moderate OSA 5 -9/h; severe OSA ≥10/h
  - adults: mild OSA 5.1-15/h; moderate OSA 15.1-30/h; severe OSA >30.1/h

Treatment
- nonsurgical: sleep hygiene, CPAP, BiPAP (bilevel positive airway pressure); weight loss in overweight/obese child with OSA
- medication: topical nasal steroids and leukotriene-receptor antagonists for mild OSA or residual sleep-disordered breathing post-adenotonsillectomy
- surgical: bilateral tonsillectomy and adenoidectomy is surgery of choice
  - if persistent OSA following tonsillectomy and adenoidectomy, consider adenoid regrowth
  - if these fail and patient not tolerant of positive airway pressure therapy, consider lingual tonsillectomy, midline posterior glossectomy, tongue suspension or other surgeries targeting areas of resistance as required; surgery may be guided by drug-induced sleep endoscopy or cineradiography-MRI to localize site of resistance

Peritonsillar Abscess (Quinsy)

Definition
- cellulitis of space behind tonsillar capsule extending onto soft palate, leading to abscess

Etiology
- bacterial: group A *Streptococcus* (GAS) (50% of cases), *S. pyogenes, S. aureus, H. influenzae*, and anaerobes

Epidemiology
- can develop from acute tonsillitis with infection spreading into plane of tonsillar bed (see Pediatrics, P64)
- unilateral
- most common in 15-30 yr age group

Quinsy Triad
- Trismus
- Uvular deviation
- Dysphonia ("hot potato voice")

Clinical Features
- trismus (due to irritation and reflex spasm of the medial pterygoid) is the most reliable indicator of peritonsillar abscess
- fever and dehydration
- sore throat, dysphagia, odynophagia, and drooling
- extensive peritonsillar swelling but tonsil may appear normal
- edema of soft palate
- uvular deviation
- dysphonia (edema → failure to elevate palate) 2° to CN X involvement
- unilateral referred otalgia
- cervical lymphadenitis

Complications
- aspiration pneumonia 2° to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

Treatment
- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 d if cultures positive for GAS
- add PO/IV metronidazole or clindamycin x 10 d if culture positive for Bacteroides
- consider tonsillectomy after second episode

Other Sources of Parapharyngeal Space Infections
- pharyngitis
- acute suppurative parotitis (see *Salivary Glands, OT30*)
- AOM
- mastoiditis (Bezold's abscess)
- odontogenic infection

Tonsillectomy

Absolute Indications
- most common indication: sleep-disordered breathing
- second most common indication: recurrent tonsillitis
- tonsillar hypertrophy causing upper airway obstruction, OSA, severe dysphagia, or cardiopulmonary complications such as cor pulmonale
- suspicion of malignancy (e.g. lymphoma, SCC)
- orofacial/dental deformity
- hemorrhagic tonsillitis

Relative Indications (To Reduce Disease Burden)
- recurrent tonsillitis with a frequency of at least 7 episodes in the past yr, at least 5 episodes per yr for 2 yr, or at least 3 episodes per yr for 3 yr with documentation in the medical record for each episode of sore throat, and 1 or more of the following: temperature >38.3°C, cervical adenopathy, tonsillar exudate, or positive test for group A β-hemolytic *Streptococcus* (Paradise Criteria)
- chronic tonsillitis with halitosis (bad breath) or sore throat ± tonsiliths/tonsilloliths (clusters of material that form in the crevices of the tonsils)
- complications of tonsillitis: quinsy/peritonsillar abscess, parapharyngeal abscess, retropharyngeal abscess
- failure to thrive

Relative Contraindications
- velopharyngeal insufficiency: overt or submucous/covert cleft of palate, impaired palatal function due to neurological or neuromuscular abnormalities
- hematologic: coagulopathy, anemia
- infectious: active local infection without urgent obstructive symptoms

Complications
- hemorrhage: primary (within 24 h); secondary (within first 7-10 d)
- odynophagia and/or otalgia; dehydration 2° to odynophagia
- infection
- atlantoaxial subluxation (Grisel's syndrome) - rare

Airway Problems in Children

DIFFERENTIAL DIAGNOSIS BY AGE GROUP

Neonates (Obligate Nose Breathers)
- extralaryngeal
  - pyriform aperture stenosis
  - septal deviation
  - choanal atresia (e.g. CHARGE syndrome)
  - nasopharyngeal dermoid, glioma, encephalocoele
  - glossoptosis: Pierre-Robin sequence, Down syndrome, lymphatic malformation, hemangioma
- laryngeal
  - laryngomalacia: most common cause of stridor in children
  - saccular cyst/laryngocele
  - vocal cord palsy (due to trauma or Arnold-Chiari malformation)
  - glottic web
  - laryngeal cleft
  - laryngeal papillomatosis
  - subglottic stenosis
- tracheal
  - TEF
  - compression by vascular structure (e.g. left pulmonary artery sling, vascular ring)
  - tracheomalacia (anterior displacement of trachealis muscle)
  - complete tracheal rings

2-3 Months
- congenital
  - laryngomalacia
  - vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
  - laryngeal papilloma
- acquired
  - subglottic stenosis: post-intubation
  - tracheal granulation: post-intubation
  - tracheomalacia: post-tracheotomy and TEF repair

Infants – Sudden Onset
- foreign body aspiration
- croup
- bacterial tracheitis
- caustic ingestion
- epiglottitis

Children and Adults
- infection
  - Ludwig's angina
  - peritonsillar/parapharyngeal abscess
  - retropharyngeal abscess
- neoplastic
  - SCC (larynx, hypopharynx (adults))
  - retropharyngeal: lymphoma, neuroblastoma
  - nasopharyngeal: carcinoma, rhabdomyosarcoma
- allergic
  - angioneurotic edema
  - polyps (suspect cystic fibrosis in children)
- trauma
  - laryngeal fracture, facial fracture
  - burns and lacerations
  - post-intubation
  - caustic ingestion
- congenital
  - lingual thyroglossal duct cyst
  - lingual tonsil hypertrophy
  - lingual thyroid

Signs of Airway Obstruction

Stridor
- note quality, timing (suggests site of stenosis)
  - inspiratory: vocal cords or above
  - biphasic: subglottis and extrathoracic trachea
  - expiratory: distal tracheobronchial tree
- body position important
  - lying prone: double aortic arch
  - lying supine: laryngomalacia, glossoptosis

Respiratory Distress
- nasal flaring
- tracheal tug
- supraclavicular and intercostal indrawing
- sternal retractions
- use of accessory muscles of respiration
- tachypnea
- cyanosis
- altered LOC

Feeding Difficulty and Aspiration
- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- laryngeal cleft → aspiration pneumonia
- TEF

Acute Laryngotracheobronchitis (Croup)

Definition
- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space is narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

Etiology
- viral: parainfluenzae I (most common), II, III, influenza A and B, RSV

Clinical Features
- age: 6 mo-3 yr
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea-lion bark)
- sternal/intercostal indrawing
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- "steeple-sign" on AP x-ray of neck
- if recurrent croup, think subglottic stenosis

Signs of Croup

The 3 Ss
Stridor
Subglottic swelling
Seal bark cough

Treatment
- nebulized epinephrine via metered-dose inhaler q1-2 h PRN (if severe croup, >2 Westley Croup Score)
- systemic corticosteroids (e.g. dexamethasone 0.5 mg/kg, prednisone)
- adequate hydration
- close observation for 3-4 h
- positive pressure ventilation, nasal trumpet, laryngeal mask airway, intubation if severe (use smaller endotracheal tube than expected for age)
- hospitalize if poor response to steroids after 4 h and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)
- if recurrent episodes of croup-like symptoms, consider bronchoscopy for definitive diagnosis

Acute Epiglottitis

Acute epiglottitis is a medical emergency

Definition
- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

When managing epiglottitis, it is important not to agitate the child, as this may precipitate complete obstruction

Etiology
- *H. influenzae* type B
- relatively uncommon condition due to *H. influenzae* type B vaccine
- common causes now include *S. pneumoniae* and *S. aureus*

Clinical Features
- any age, most commonly 1-4 yr
- rapid onset
- toxic-looking, fever, anorexia, restlessness
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up ("tripod" posture), open mouth, drooling, tongue protruding, sore throat, dysphagia

Thumb sign: cherry-shaped epiglottic swelling with loss of the normal air space of the vallecula seen on lateral neck radiograph

Investigations and Management
- examining the throat may lead to potential laryngospasm and airway compromise; ensure an anesthesiologist/otolaryngologist is present and make preparations for intubation or tracheotomy prior to any manipulation
- WBC (elevated); blood and pharyngeal cultures after intubation
- lateral neck radiograph (only done if patient stable) shows "thumb sign"

Treatment
- secure airway
- IV access with hydration
- antibiotics: IV cefuroxime, cefotaxime, or ceftriaxone (10-14 d course should be completed)
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis

Subglottic Stenosis

Congenital
- diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage), or smaller than average size for age as determined by Myer-Cotton grading system

Acquired
- following prolonged, repeated, or traumatic intubation
  - most commonly due to endotracheal intubation; nasal intubation is less traumatic and preferred in long-term intubation, as it puts less pressure on the subglottis (tube sits at different orientation) and there is less movement
  - subglottic stenosis is related to duration of intubation and endotracheal tube size resulting in pressure necrosis and subsequent scar formation
- can also be due to foreign body, infection (e.g. TB, diphtheria, syphilis), or chemical irritation

Clinical Features
- biphasic stridor
- respiratory distress
- recurrent/prolonged croup

Diagnosis
- rigid laryngoscopy and bronchoscopy done under general anesthesia

Treatment
- if soft stenosis: divide tissue with knife or laser, dilate with balloon ± steroids
- if firm stenosis: laryngotracheoplasty

Laryngomalacia

Definition
- short aryepiglottic folds, omega-shaped epiglottis, redundant mucosa over arytenoids
- caused by indrawing of supraglottis on inspiration, leading to breathing against closed glottis, causing laryngopharyngeal reflux of acid

Laryngomalacia is the most common cause of stridor in infants

Clinical Features
- high-pitched inspiratory stridor at 1-2 wk
- stridor is constant or intermittent and more pronounced with feeding, crying, agitation, being in supine position, or following an URTI
- usually mild, but can be associated with cyanosis or feeding difficulties when severe, leading to failure to thrive

Treatment
- observation ± proton pump inhibitor (to break the acid reflux cycle that leads to edema and worse airway obstruction) is usually sufficient, as symptoms spontaneously subside by 12-18 mo in >90% of cases
- if severe, division of the aryepiglottic folds (supraglottoplasty) provides relief

Foreign Body

Ingested
- usually stuck at cricopharyngeus muscle
- coins, toys, batteries (emergency)
- presents with drooling, dysphagia, stridor if very large

Foreign body inhalation is the most common cause of accidental death in children

Aspirated
- usually stuck at right main bronchus
- peanuts, carrot, apple core, popcorn, balloons
- presentation
  - stridor if lodged in trachea (beware of the silent child as there may be complete obstruction)
  - unilateral "asthma" if bronchial, therefore often misdiagnosed as asthma
  - if completely occluded airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax, death

Button batteries MUST be ruled out as a foreign body (vs. coins) as they are lethal and can erode through the esophagus. Batteries have a halo sign around the rim on AP x-ray and a step deformity on lateral x-ray

Diagnosis and Treatment
- sudden onset, not necessarily febrile or elevated WBC
- any patient with suspected foreign body should be kept NPO immediately
- older patient: inspiratory-expiratory chest x-ray (if patient is stable)
- younger patient: right and left decubitus chest x-rays. Lack of lung deflation while resting on dependent side suggests foreign body blocking bronchus
- bronchoscopy or esophagoscopy with removal

Deep Neck Space Infection

Definition
- most commonly arise from an infection of mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
- often a rapid onset and may progress to fatal complications

Etiology
- usually mixed aerobes and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes

Clinical Features
- sore throat or pain and trismus
- dysphagia and odynophagia
- stridor and dyspnea
- late findings may include dysphonia and hoarseness
- swelling of the face and neck, erythema
- asymmetry of the oropharynx with purulent oral discharge
- fever, lymphadenopathy

These investigations should be obtained carefully and the surgeon should consider accompanying the patient, as the worst place to lose an airway is during imaging

Ludwig's angina is the prototypical infection of the submandibular and sublingual space

Diagnosis
- CBC with differential
- lateral cervical view plain radiograph
- CT
- MRI

Treatment
- secure the airway
- surgical drainage
- maximum doses of IV systemic antimicrobials regimens according to the site of infection

Common Medications

Table 22. Antibiotics

Generic Name (Brand Name)	Dose	Indications	Notes
amoxicillin (Amoxil®, Amoxi®, Amox®)	Adult: 500 mg PO TID Children: 75-90 mg/kg/d in 2 divided doses	*Streptococcus, Pneumococcus, H. influenzae, Proteus* coverage	May cause rash in patients with infectious mononucleosis
piperacillin with tazobactam (Zosyn®)	3 g PO q6 h	Gram-positive and negative aerobes and anaerobes plus *Pseudomonas* coverage	May cause pseudomembranous colitis
ciprofloxacin (Cipro®, Ciloxan®)	500 mg PO BID	*Pseudomonas*, *Streptococcus*, methicillin-resistant *Staphylococcus aureus* (MRSA), and most Gram-negative; no anaerobic coverage	Animal studies suggest that systemic quinolones may cause cartilage necrosis in children
erythromycin (Erythrocin®, EryPed®, Staticin®, T-Stat®, Erybid®, Novorythro Encap®)	500 mg PO QID	Alternative to penicillin	Ototoxic

Table 23. Otic Drops

Generic Name (Brand Name)	Dose	Indications	Notes
ciprofloxacin (Ciprodex®)	4 gtt in affected ear BID	For OE and complications of OM *Pseudomonas*, streptococci, MRSA, and most Gram-negative; no anaerobic coverage	
neomycin, polymyxin B sulfate, and hydrocortisone (Cortisporin Otic®)	5 gtt in affected ear TID	For OE Used for inflammatory conditions which are currently infected or at risk of bacterial infections	May cause HL if placed in inner ear
hydrocortisone and acetic acid (VoSol HC®)	5-10 gtt in affected ear TID	For OM	Bactericidal by lowering pH
tobramycin and dexamethasone (TobraDex®)	5-10 gtt in affected ear BID	For chronic suppurative OM	Risk of vestibular or cochlear toxicity
Locacorten-Vioform Ear Drops®	2-3 gtt in affected ear BID	For OE, Otomycosis	

Table 24. Nasal Sprays

Generic Name (Brand Name)	Indications	Notes
Steroid		
flunisolide (Rhinalar®), budesonide (Rhinocort®), triamcinolone (Nasacort®) beclomethasone (Beconase®), mometasone furoate, monohydrate (Nasonex®), fluticasone furoate (Avamys®, Flonase®), ciclesonide (Omnaris®)	Allergic rhinitis Chronic sinusitis	Requires up to 4 wk of consistent use to have effect Long-term use Long-term use may dry nasal mucosa and cause minor bleeding Patient should stop if epistaxis May sting Flonase® and Nasonex® not absorbed systemically
Antihistamine		
levocabastine (Livostin®)	Allergic rhinitis	Immediate effect Discontinue if no effect by day 3 Use during allergy season
Decongestant		
xylometazoline (Otrivin®), oxymetazoline (Dristan®), phenylephrine (Neosynephrine®)	Acute sinusitis Rhinitis	Careful if patient has HTN Short-term use (<5 d) If long-term use, can cause decongestant addiction (i.e. rhinitis medicamentosa)
Antibiotic/Decongestant		
framycetin, gramicidin, phenylephrine (Soframycin®)	Acute sinusitis	
Anticholinergic		
ipratropium bromide (Atrovent®)	Vasomotor rhinitis	Careful not to spray into eyes as it can cause burning or precipitate narrow angle glaucoma Increased rate of epistaxis when combined with topical nasal steroids
Lubricants		
saline, NeilMed®, Rhinaris®, Secaris®, Polysporin®, Vaseline®	Dry nasal mucosa	Use PRN Rhinaris® and Secaris® may cause stinging
Combination		
azelastine hydrochloride (antihistamine) and fluticasone propionate (steroid) (Dymista®)	Allergic rhinitis	

Source: Dr. MM Carr

Landmark Otolaryngology - Head and Neck Surgery Trials

Trial Name	Reference	Clinical Trial Details
Acute Otitis Media		
Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children	NEJM 2016; 375:2446-2456	**Title**: Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children **Purpose**: To study the potential of limiting the duration of antimicrobial treatment among children with acute otitis media to prevent antimicrobial resistance. **Methods**: Children with acute otitis media were assigned to 2 groups. 1 group received amoxicillin-clavulanate for 10 d, the other group received a reduced duration of 5 d. Rate of clinical response, recurrence, and nasopharyngeal colonization were measured. **Results**: Children treated with amoxicillin-clavulanate for 5 d had higher rates of clinical failure than those treated for the full duration. Mean symptoms scores from days 6-14 were 1.61 in the 5 d group and 1.34 in the 10 d group. **Conclusions**: 10 d of amoxicillin-clavulanate had more favourable outcomes and no increase in adverse events or antimicrobial resistance compared to a 5 d course in children ages 6 mo-2 yr.
Effect of Antimicrobial Treatment of Acute Otitis Media on the Daily Disappearance on Middle Ear Effusion	JAMA Pediatr. 2014;168(7):635-641	**Title**: Effect of Antimicrobial Treatment of Acute Otitis Media on the Daily Disappearance on Middle Ear Effusion **Purpose**: To study the effect of antimicrobial treatment on the duration of MEE and hearing impairment. **Methods**: Children were assigned to either have 40 mg/kg of amoxicillin-clavulanate or a placebo mixture for 7 d. The primary outcome measure was time till disappearance of MEE. **Results**: MEE disappeared 2 wk earlier in the antimicrobial group than in the placebo group (2.7 wk vs. 4.7 wk, respectively). **Conclusions**: Treatment with amoxicillin-clavulanate reduced the duration of middle ear effusion compared to placebo in children with acute otitis media.
Head and Neck Malignancy		
Elective vs. Therapeutic Neck Dissection in Node-Negative Oral Cancer	NEJM 2015; 373(6):521-9	**Title**: Elective vs. Therapeutic Neck Dissection in Node-Negative Oral Cancer **Purpose**:To evaluate survival after elective neck dissection vs. therapeutic neck dissection in patients with lateralized stage T1 or T2 oral squamous-cell carcinomas. **Methods**: A prospective, randomized, controlled trial that evaluated survival after elective node dissection vs. therapeutic node dissection. Overall survival and disease-free survival were used as primary and secondary endpoints, respectively. **Results**: At 3 yr, elective node dissection resulted in more survival (80%), than therapeutic neck dissection (67.5%). As well, at 3 yr, elective node dissection patients had a higher rate of disease free survival compared to those in the therapeutic surgery group (69.5% vs. 45.9%). **Conclusions**: Among patients with early-stage OSCC, elective neck dissection resulted in higher rates of overall and disease-free survival.
PET-NECK	NEJM 2016; 374:1444-1454	**Title**: PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer **Purpose**: To compare the usefulness of planned neck dissection versus PET-CT-guided surveillance in patients with nodal stage N2 or N3 SCC. **Methods**: Patients with N2 or N3 neck disease were randomly assigned to either a neck dissection (planned surgery group) or PET-CT 12 weeks after chemoradiotherapy completion (surveillance group). The primary endpoint was overall survival. **Results**: The 2-yr survival rate was 84.9% (95% CI, 80.7 to 89.1) in the surveillance group and 81.5% (95% CI, 76.9 to 86.3) in the surgery group. The hazard ratio slightly favoured PET-CT-guided surveillance and indicated non-inferiority (upper boundary of the 95% CI for the hazard ratio, <1.50; P=0.004). **Conclusions**: PET-CT-guided surveillance is non-inferior to planned neck dissection for overall survival in N2 or N3 SCC of the head and neck.
CheckMate 141	NEJM 2016; 375:1856-1867	**Title**: Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck **Purpose**: To compare the overall survival of patients with platinum-refractory SCC of the head and neck treated with nivolumab versus standard therapy. **Methods**: Patients with recurrent SCC of the head and neck and disease progression within 6 mo after platinum-based chemotherapy received either nivolumab or standard systemic therapy (methotrexate, docetaxel, or cetuximab). The primary endpoint was overall survival. **Results**: Median overall survival was 7.5 mo (95% CI, 5.5 to 9.1) in the nivolumab group compared to 5.1 mo (95% CI, 4.0 to 6.0) in the standard therapy group. Survival is significantly longer with nivolumab (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; P=0.01). **Conclusions**: Treatment with nivolumab resulted in longer overall survival than treatment with standard therapy in platinum-refractory, recurrent squamous-cell carcinoma of the head and neck.
Sleep-Disordered Breathing		
KATE	JAMA Otolaryngol Head Neck Surg. 2020;146(7):647-654	**Title**: Effectiveness of Adenotonsillectomy vs. Watchful Waiting in Young Children With Mild to Moderate Obstructive Sleep Apnea: A Randomized Clinical Trial **Purpose**: To determine whether adenotonsillectomy is more effective than watchful waiting for treating healthy children with mild to moderate OSA. **Methods**: 60 children ages 2 to 4 with mild to moderate OSA were randomized to either adenotonsillectomy or watchful waiting. The primary outcome was the difference in mean obstructive apnea-hypopnea index (OAHI) score change between the two groups. **Results**: Both groups had a reduced mean OAHI score with a small intergroup difference (−1.0; 95% CI, −2.4 to 0.5). Children with moderate OSA showed a meaningful intergroup difference in mean OAHI score change, favouring adenotonsillectomy (−3.1; 95% CI, −5.7 to −0.5). **Conclusions**: Otherwise healthy children ages 2-4 with mild OSA may benefit from watchful waiting, while children with moderate OSA should be considered for surgical treatment.
CHAT	NEJM 2019; 20(9):1273-1285	**Title**: A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea **Purpose**: To investigate the benefits of adenotonsillectomy vs. supportive care on children with obstructive sleep apnea. **Methods**: Children ages 5-9 yr, with obstructive sleep apnea syndrome were randomized to adenotonsillectomy or a strategy of watchful waiting. Polysomnographic, cognitive, behavioural, and health outcomes were assessed at baseline and again at 7 mo. **Results**: Attention and executive function scores from baseline did not change significantly in the adenotonsillectomy group vs. the watchful waiting group (7.1±13.9 vs. 5.1±13.4, respectively). Significant differences from baseline in behavioural, and quality of life were found in the adenotonsillectomy group. Normalization of polysomnographic findings were found in more of the adenotonsillectomy than the watchful waiting group (79% vs. 46%). **Conclusions**: Surgical treatment for obstructive sleep apnea in children ages 5-9 did not significantly improve attention or executive function but did improve behaviour, quality of life, and polysomnographic findings compared to watchful waiting.

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PM Palliative Medicine

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Acronyms

ADLs	activities of daily living	CPR	cardiopulmonary resuscitation	EOL	end-of-life	POA Power of Attorney
AND	allow natural death	DNR	do not resuscitate	SDM	substitute decision maker	

Palliative Approach to Care

Palliative Care

Definition

- an approach that seeks to improve the quality of life of patients and their families facing a life-threatening illness, through the prevention and relief of suffering
- applicable at any time during a life-limiting illness, and may be delivered in conjunction with life-prolonging or curative intervention
- palliative approach to care is not just for EOL

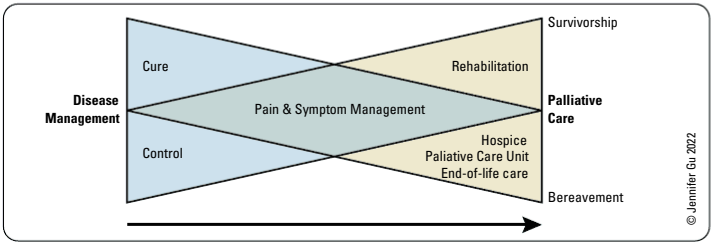


Figure 1. Palliative care enhanced model
Courtesy of Dr. Philippa Hawley

Palliative Care Assessment

- comprehensive and includes physical, psychosocial, and spiritual domains of care
- complete medical history – includes determining the patient's knowledge of their illness, determining who their SDM is and their goals of care
- physical symptom assessment – patient's opinion of severity is the gold standard, and may be measured using assessment tools such as the Edmonton Symptom Assessment System (ESAS)
- functional status assessment – ability to perform ADLs, measured using tools such as the Palliative Performance Scale (PPS)
- psychosocial symptom assessment – anxiety, depression, family/caregiver distress, and cultural/financial status
- spiritual assessment – religious beliefs, values, coping mechanisms, and distress
- medication review – limit polypharmacy

Pain and Symptom Management

Assessment Tools

- **Edmonton Symptom Assessment System (ESAS):** a tool used to screen for common symptoms seen in palliative care. Patients/caregivers are asked to rate the intensity of symptoms from 0 to 10 on a numeric rating scale where 0 represents the absence of the symptom and 10 represents the worst severity of the symptom. Assesses: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and "other problems" associated with specific conditions such as pruritus in liver disease and cough in lung disease. The ESAS provides a measure of symptom burden and allows for tracking the efficacy of interventions over time

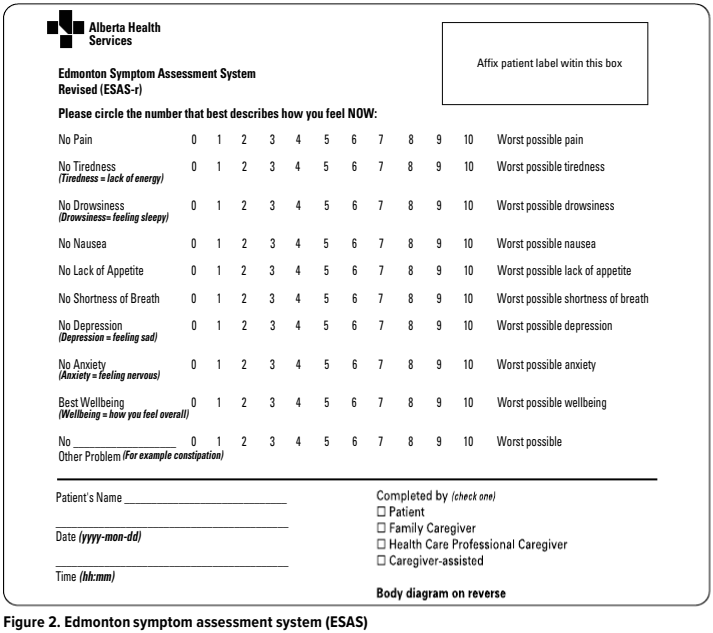
See Landmark Palliative Care Trials table for more information on the study by Temel et al., 2010 which details the benefits of early palliative care for patients with metastatic Non–Small-Cell Lung Cancer.

See Landmark Palliative Care Trials table for more information on the ENABLE II trial, which details the effect of a nursing-led intervention on quality of life (QoL), symptom intensity, mood, and resource use in patients with advanced gastrointestinal tract, lung, genitourinary tract, or breast cancer.

See Landmark Palliative Care Trials table for more information on the ENABLE III trial, which assesses the impact of early vs. delayed initiation of concurrent palliative oncology care on patient QoL, symptom impact, 1-yr survival, and resource use.

Associations Between End-of-Life Discussions, Patient Mental Health, Medical Care Near Death, and Caregiver Bereavement Adjustment
JAMA 2008;300(14):1665-73
Purpose: To determine whether end of life discussions with a physician are associated with fewer aggressive interventions.
Methods: Longitudinal cohort study of 332 patient and caregiver dyads. Patients were followed from admission to death. Outcomes of interest were medical interventions including ventilation, resuscitation, and hospice in the final week of life.
Results: 123 patients reported having an end-of-life discussion. Discussions were not associated with higher rates of Major Depressive Disorder (MDD). End-of-life discussions were associated with earlier admissions to hospice (65.6% vs. 44.5%), lower rates of ventilation (1.6% vs. 11%), resuscitation (0.8% vs. 6.7%), and ICU admission (4.1% vs. 12.4%).
Conclusions: End-of-life discussions result in less aggressive medical care and earlier hospice admission.

Associations Between Palliative Care and Patient and Caregiver Outcomes: A Systematic Review and Meta-analysis
JAMA 2016;316(20):2104-2114
Purpose: To determine the association of palliative care with quality of life (QoL), symptom burden, survival, and other outcomes for people with life-limiting illness and for their caregivers.
Methods: Systematic review and meta-analysis of RCTs (n=43) of palliative care interventions in adults with life-limiting illness.
Results: In the meta-analysis, palliative care was associated with statistically and clinically significant improvements in patient QoL (standardized mean difference 0.46, 95% CI 0.08 to 0.83) and symptom burden (standardized mean difference -0.66, 95% CI -1.25 to -0.07) at the 1 to 3 mo follow up. There was no association between palliative care and survival (HR 0.90, 95% CI 0.69 to 1.17).
Conclusions: Palliative care interventions were associated with improvements in patient QoL and symptom burden. Findings for caregiver outcomes were inconsistent.



Alberta Health Services

Affix patient label witin this box

Edmonton Symptom Assessment System Revised (ESAS-r)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
No Drowsiness *(Drowsiness= feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible lack of appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst possible wellbeing
No _____ Other Problem *(For example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst possible

Patient's Name _____

_____

Date *(yyyy-mon-dd)*

_____

Time *(hh:mm)*

Completed by *(check one)*
☐ Patient
☐ Family Caregiver
☐ Health Care Professional Caregiver
☐ Caregiver-assisted

Body diagram on reverse

Figure 2. Edmonton symptom assessment system (ESAS)
Adapted from: Alberta Health Services Edmonton Zone Palliative Care Program. Edmonton Symptom Assessment System-revised (ESAS-r): Administration Manual. Covenant Health Palliative Institute

- **Palliative Performance Scale (PPS):** a tool used to assess functional status. Assesses 5 components: ambulation, activity and evidence of disease, self-care, intake, and consciousness level. Has prognostic value in patients with advanced cancer. PPS is read by starting at the 'ambulation' column and dropping down the rows until the patient's description is met. Then, moving columns to the right and down if needed, but not up, as you assess the patient's abilities in each column with the lower number scored being the overall PPS

Table 1. Palliative Performance Scale

PPS Level	Ambulation	Activity and Evidence of Disease	Self-Care	Intake	Conscious Level
100%	Full	Normal activity and work No evidence of disease	Full	Normal	Full
90%	Full	Normal activity and work Some evidence of disease	Full	Normal	Full
80%	Full	Normal activity with effort Some evidence of disease	Full	Normal or reduced	Full
70%	Reduced	Unable to do normal job/work Significant disease	Full	Normal or reduced	Full
60%	Reduced	Unable to do hobby/housework Significant disease	Occasional assistance necessary	Normal or reduced	Full or confusion
50%	Mainly sit/lie	Unable to do any work Extensive disease	Occasional assistance necessary	Normal or reduced	Full or confusion
40%	Mainly in bed	Unable to do most activities Extensive disease	Mainly assisted	Normal or reduced	Full or drowsy ± confusion
30%	Totally bed bound	Unable to do any activities Extensive disease	Total care	Normal or reduced	Full or drowsy ± confusion
20%	Totally bed bound	Unable to do any activities Extensive disease	Total care	Minimal to sips	Full or drowsy ± confusion
10%	Totally bed bound	Unable to do any activities Extensive disease	Total care	Mouth care only	Drowsy or coma ± confusion
0%	Death	—	—	—	—

Adapted from: Medical care of the dying, 4th ed. Victoria: Victoria Hospice Society, 2006. Version 2

Table 2. Symptom Management

Symptom	Non-Pharmacologic Management	Pharmacologic Management
Constipation	Rule out obstruction, impaction, anorectal disease, and spinal cord pathology Hydration, orally where possible Increase mobility	Stimulant laxatives (senna), osmotic laxatives (lactulose)
Dyspnea	Elevate head of bed, eliminate allergens, and open window/use fan	Oxygen, bronchodilators, opioids (e.g. morphine, hydromorphone)
Hiccups	wallow 1 tsp of dry sugar, or dry bread (nasopharyngeal stimulation/vagus nerve stimulation) Rebreathing into paper bag (increases partial pressure of CO_2)	Dopamine antagonists (e.g. chlorpromazine, haloperidol, metoclopramide) Smooth muscle relaxants (e.g. hyoscine butylbromide (Buscopan®), baclofen
Nausea and Vomiting	Frequent and small meals, avoid offensive strong odours, and treat constipation if present	Raised ICP: dexamethasone Anticipatory nausea, anxiety: lorazepam Vestibular disease, vertigo: dimenhydrinate Drug induced, hepatic, or renal failure: prochlorperazine, haloperidol Gastroesophageal reflux disease: proton pump inhibitor (PPI), H2 antagonist Gastric stasis: metoclopramide Bowel obstruction: metoclopramide, dexamethasone, octreotide
Pain	Hot and cold compresses, art/music therapy, relaxation techniques, physical therapy, massage therapy, acupuncture, and cognitive behavioural therapy (CBT)	Nociceptive pain: non-opioids (NSAIDs, acetaminophen), weak opioids (e.g. codeine, tramadol), strong opioids (e.g. morphine, hydromorphone, oxycodone, fentanyl) Neuropathic pain: anticonvulsants (gabapentin, pregabalin), antidepressants (tricyclic antidepressants (TCAs)), selective serotonin reuptake inhibitors (SSRIs), steroids (dexamethasone) Bony pain: NSAIDs, acetaminophen and/or opioids, depending on pain severity; bisphosphonates, radiation therapy For more information on pain management, see Anesthesia, A25
Pruritus	Bathe with tepid water, and avoid soap and bath oils	Antihistamines, phenothiazines, topical low potency corticosteroids, calamine lotion
Fatigue	Modify environment and activities to decrease energy expenditure Optimize fluid and electrolyte intake Educate and support patient and family Exercise	Treat underlying condition(s) if present (e.g. methylphenidate, dexamethasone)
Psychiatric	CBT, support groups, art/music therapy	Agitation: neuroleptics Confusion/Delirium: treat underlying etiology if possible. Otherwise manage with neuroleptics (e.g. haloperidol) Depression: standard SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs) may be too slow depending on patient prognosis, may consider psychostimulants (e.g. methylphenidate, ketamine)
Oropharyngeal Secretions (Death Rattle)	Reassure family that patient is not in respiratory distress Oral suctioning, avoid deep suctioning Discontinue unnecessary IV solutions Re-positioning (on side, elevated) Monitor for adverse effects (xerostomia, delirium, sedation)	Anticholinergic agents used to dry secretions Hyoscine hydrobromide (scopolamine) SC or transdermal, glycopyrronium (glycopyrrolate) SC Glycopyrronium is typically preferred because of less central effects compared to scopolamine as it does not cross the blood-brain-barrier

Source: J Am Geriatr Soc 2002;50:S205-S224 and On Continuing Practice 1993;20:20-25 and Am Fam Physician 2009;79(12):1059-1065

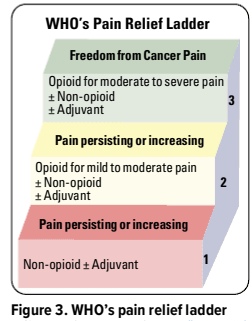


Figure 3. WHO's pain relief ladder
WHO's Pain Relief ladder, available from: https://www.who.int/cancer/palliative/painladder/en/

Pain Management

- see Anesthesia, A25

Pain Syndromes

- see Neurology, N43

Care of the Dying Patient

General Predictors of Decline in the Final Months of Life

- decreasing activity – functional performance status declining, limited self-care, in bed or chair 50% of day, and increasing dependence in most ADLs
- co-morbidity – biggest predictive indicator of mortality and morbidity
- general physical decline and increasing need for support
- advanced disease – unstable, deteriorating complex symptom burden
- decreasing response to treatments, decreasing reversibility
- choice of no further active treatment
- progressive weight loss (>10%) in the past 6 mo
- repeated unplanned/crisis admissions
- sentinel event (e.g. serious fall, bereavement, transfer to nursing home)
- serum albumin <25 g/L
- considered eligible for terminal illness disability benefits

Changes in the Last Hours of Life

- decreased level of consciousness
- changes in breathing pattern (Cheyne-Stokes breathing)
- airway secretions causing noisy breathing
- inability to swallow safely and increased risk of aspiration
- delirium (terminal restlessness)
- mottling of the hands, feet, and legs
- cool extremities

Care of the Patient in the Final Days of Life

- educate the family on the physiological changes in the dying process and discuss potentially difficult decisions (e.g. hydration)
- have a plan in place for an expected death in the home (EDITH), who to call (not 911), and how the death certificate will be made available to the funeral home
- if the patient is unable to swallow, administer essential medications by non-oral routes (e.g. SC, gastrostomy tube, IV, nasal, oral and rectal transmucosal, transdermal), with SC being the preferred option
- discontinue non-essential and potentially inappropriate medications (e.g. for primary and secondary prevention); review other measures such as IV/SC hydration and consider stopping if no longer beneficial

Psychosocial and Spiritual Needs

- palliative care assessment includes addressing psychosocial and spiritual well-being
- psychosocial needs pertain to the psychological and emotional well-being of patients and their carers, including concerns such as self-esteem, adaptation to illness, communication, and social functioning
- patient's psychosocial experience is further shaped by the experience of pain and other symptoms related to the condition and its treatment
- spiritual needs pertain to the manner in which the patient expresses meaning, value, and purpose in life. May include, but is not limited to, religious practices or philosophical reflection

Approach to Assessing Psychosocial and Spiritual Needs

- holistic psychosocial assessment can help identify supports a person might need during their illness. Psychosocial issues can manifest as physical symptoms (e.g. pain, constipation, nausea). Therefore, it is important to be aware of physiological symptoms that may indicate depression and anxiety
- mental and emotional needs – fear, worry, insomnia, panic, anxiety, nervousness, or lack of energy
- social needs – family dynamics, communication, social and cultural networks, perceived social support, finances, intimacy, living arrangements, caregiver availability, etc.
- cultural needs – beliefs and preferences, linguistic needs, health behaviours, traditions, rituals, and cultural barriers to accessing health
- to further explore questions about spirituality, the FICA spiritual assessment tool may be used
- **FICA** – the four components to cover during a spiritual care assessment are: Faith or beliefs, Importance of those beliefs, patient's participation in a religious or spiritual Community, and how healthcare providers should Address the patient's health care issues

Interprofessional Care Plan for Psychosocial and Spiritual Needs

- interprofessional team of care providers including physicians, nurse practitioners, nurses, social workers, psychologists, chaplains, spiritual advisors, pharmacists, and physical and occupational therapists assist in the following interventions:
- home care, respite care, social networks and activities, problem-solving and education, one-on-one therapy, and group work

See Landmark Palliative Care Trials table for more information on the study by Naylor et al., 1999, which details the effectiveness of advanced practice nurse-centered discharge planning and home follow-up intervention for older aged individuals at risk for hospital readmissions.

5 Dimensions of a Good Death
Quality End-Of-Life Care: Patients' Perspectives JAMA 1999;281:163-168

Pain/symptom management
Avoiding prolongation of dying
Achieving a sense of control
Relieving burden on others
Strengthening relationships with loved ones

Does Feeding Tube Insertion and its Timing Improve Survival
J Am Geriatr Soc 2013;60(10):1918-1921
Purpose: To examine survival rates with and without a percutaneous endoscopic gastrostomy (PEG) feeding tube, and to determine if timing of feeding tube insertion affects survival.
Methods: Prospective cohort study and multivariate analysis of nursing home residents (n=36,492) with advanced cognitive impairment from dementia and new problems eating.
Results: No difference in survival was found between nursing home residents who had a feeding tube inserted within 1 yr of developing eating problems compared to those who had no tube inserted. The timing of PEG tube insertion relative to onset of eating problems was not associated with improved survival post feeding tube insertion.
Conclusions: Neither insertion of PEG feeding tubes nor the timing of insertion improves survival.

See Landmark Clinical Trials table for more information on the effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnea.

See Landmark Clinical Trials table for more information on the safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness.

End-of-Life Decision Making

Types of Discussions

Advance Care Planning Discussion
- it involves a mentally capable patient:
  1. identifying their SDM or POA. If a patient chooses a POA, then the POA document can be completed
  2. discussing one's values, beliefs, and wishes for future health care, should one become incapable of making health care decisions
  3. if the patient is not capable, a discussion about advance care planning should occur with their SDM or POA present

Goals of Care Discussion
- exploratory discussion where the health care provider and patient discuss the patient's current medical issues, their understanding of their illness, and possible treatments and outcomes. May or may not include discussion about code status

Code Status Discussion
- discussion with patient about level of intervention they would want in the event of cardiac or respiratory arrest
  - **full code**: patient would like to receive CPR, defibrillation, and life support
  - **Do Not Resuscitate (DNR):** patient would not like to receive CPR or life support, only active medical management
  - **comfort measures:** patient would not like to receive CPR, life support, or active medical management
  - **Allow Natural Death (AND):** alternative term to DNR. Often a gentler term to help with the discussion
  - CPR is rarely effective in the patient with advanced incurable illness
  - DNR order is almost always consistent with palliative goals of care

When to Initiate EOL Care Discussions
- recent hospitalization for serious illness, or during a transition in care
- severe progressive medical condition(s)
- death expected within 6-12 mo
- patient rewritten will and/or spiritual wishes
- if the patient requests medical assistance in dying (MAID)

Power of Attorney for Personal Care
- see Ethical, Legal, and Organizational Medicine, ELOM15

Factors Considered Important at the End of Life by Patients, Family, Physicians, and other Care Providers
JAMA 2000;284(19):2476-2482
Purpose: To determine what patients, families, and health care practitioners view as important at the end of life.
Methods: Cross-sectional, stratified random national survey of seriously ill patients (n=340), recently bereaved family (n=332), physicians (n=361), and other care providers (n=429) to assess importance of 44 attributes of quality at the end of life and rankings of 9 major attributes.
Results: Twenty-six items were consistently rated as important across all 4 groups, including pain and symptom management, preparation for death, achieving a sense of completion, decisions about treatment preferences, and being treated as a "whole person". Freedom from pain was ranked as the most important attribute and dying at home was ranked as the least important attribute.
Conclusions: Although there was consistency across some attributes of quality at the end of life, other factors are important and differ by role and by individual.

Communication

- strong communication is critical in all areas of medicine. This is especially true in palliative care, where difficult decisions must be made regarding goals of care, EOL care, and disclosure of information
- be cognizant of how a patient's (and their family's) beliefs, values, and wishes may impact their decision making and/or their emotional response during palliative care conversations
- use both verbal and non-verbal means of communicating empathy and caring to build rapport, and help de-escalate the intense emotions that patients may experience including anger, grief, and feeling overwhelmed

Approach to Communicating Bad News

SPIKES
S – Setting up the interview: create privacy by bringing the patient to a quiet and comfortable environment. Ensure you have enough time to have an extended conversation with the patient. Ask them if they wish for family members or other supports to be present
P – assess Perception: what does the patient and/or their family understand about their illness at present? Use open-ended questions and fill any major gaps to ensure mutual understanding
I – Invitation: how does the patient wish to hear the information? How many details do they want? Do they want to first understand the process that led the care team to their diagnosis/prognosis/treatment decision, or do they just want to hear the news upfront
K – Knowledge sharing: provide the information based on the preferences expressed in the "invitation" section in small segments using non-technical terms
E – Emotions: respond to the patient's/family's emotions. Allow them time to process the information. Silence is okay. Offer to answer any questions they may have, but also recognize that some patients may wish to discuss further details at a later time
S – Strategy and Summary: if the patient and their family are comfortable, summarize the conversation and discuss next steps

Efficacy of Communication Skills Training for Giving Bad News and Discussing Transitions to Palliative Care
JAMA Intern Med 2007;167:453-460
Purpose: To evaluate the efficacy of a residential communication skills workshop (Oncotalk) for medical oncology fellows in changing observable communication behaviours.
Methods: Medical oncology fellows' (n=115) communication skills before and after participation in the Oncotalk workshop, which dealt with delivering bad news and discussing transitions to palliative care, were assessed during standardized patient encounters.
Results: Fellows had improved in skills in delivering bad news (P<0.001) and discussing transitions to palliative care (P<0.001) after attending Oncotalk workshops.
Conclusions: Oncotalk is a successful teaching model for improving communication skills in postgraduate medical trainees.

Estimating Life Expectancy

- when asked about prognosis, be wary of being overly specific
- use time frames such as hours to days, days to weeks, weeks to many weeks, or months
- clinicians consistently overestimate survival when prognosticating

Extent and Determinants of Error in Doctors' Prognoses in Terminally Ill Patients: Prospective Cohort Study
BMJ 2000;320(7233):469-472
Purpose: To describe doctors' prognostic accuracy in terminally ill patients and to evaluate the determinants of that accuracy.
Methods: Prospective cohort study of 343 doctors who provided survival estimates for 468 terminally ill patients at the time of hospice referral. Main outcome measures were the estimated and actual survival of patients.
Results: Median survival was 24 d. Only 20% (92/468) of predictions were accurate (within 33% of actual survival); 63% (295/468) were overly optimistic and 17% (81/468) were overly pessimistic. Overall, doctors overestimated survival by a factor of 5.3.
Conclusions: Doctors are systematically optimistic in estimating prognosis for terminally ill patients. This phenomenon may adversely affect the quality of care given to patients near the end of life.

Collaboration

Interprofessional Team

- interprofessional team may include the following members:
  - physicians: may be primary care providers, or have specialty training in palliative care; they provide medical management and symptom relief
  - nurses: provide patient education in addition to clinical nursing; often with advanced practices in setting of hospice or home care
  - social workers/case managers: facilitate advance care planning conversations and other psychosocial interventions for patients and their families
  - pharmacists: timely provision of medications, assessment of medication plans
  - occupational therapists: identify important life roles and activities to patients, and address barriers to performing these activities
  - physiotherapists: optimize patient comfort by maintaining physical function during disease progression
  - dieticians: optimize a nutritional plan focused on the patient's needs and wishes
  - spiritual care workers: provide spiritual and religious care for persons with life-limiting disease
- all members of the palliative care team provide assessment of palliative care needs through the use of validated tools such as the ESAS and the PPS
- palliative care team collaborates through ongoing care conversations with the patient and their family to discuss the patient's condition, course of illness, treatment options, goals, and plan of care

Suffering

Definition

- a multidimensional experience of severe distress that diminishes an individual's ability to find peace in their present situation, with contributions from physical symptoms, psychological distress, existential concerns, and social-relational worries

Key Points

- suffering can occur at any moment within the palliative context
- suffering is subjective and unique to the patient
- anguish and despair are justifiable responses to difficult human situations
- patients may suffer not only from illness, but also from treatments
- suffering is not confined to physical symptoms
- it is impossible to anticipate the source of someone's suffering

Sources of Suffering

- **physical concerns**
  - impaired activities
  - loss of physical independence
  - symptoms (e.g. pain, tiredness, poor sleep, loss of appetite)
- **social-relational concerns**
  - family distress or dysfunction
  - burden on others
- **psychological concerns**
  - fear or dread of the unknown
  - loss of balance and control
  - difficulty accepting the situation
  - overwhelmed by life circumstances
  - comorbid depression and anxiety
- **spiritual concerns**
  - unfulfilled needs of love, virtue, faith, and/or hope
  - questioning meaning of life or death
  - anger towards a higher being (as defined by the individual)
  - viewing illness as punishment
- **existential concerns**
  - loss of dignity
  - desire for death
  - loss of will to live

Options to Relieve Refractory Suffering

- **palliative sedation therapy**: the use of pharmacological agents to reduce consciousness. Only considered in patients who have been diagnosed with advanced progressive illnesses and reserved for treatment of intolerable and refractory symptoms
- **medical assistance in dying (MAID):** in Canada, a specific process that occurs when a mentally competent patient makes a written request to end one's life. The patient is interviewed by 2 different clinicians, one of which is the MAID provider. A physician or nurse practitioner administers medications that cause a person's death or the patient is prescribed medications to self-administer that will cause one's own death
  - there are currently 2 pathways to MAID in Canada; pathway 1 where death is foreseeable and pathway 2 where the patient has a serious and incurable illness, disease, or disability but death is not immediately foreseeable
  - recent changes have also included a waiver of final consent in situations where the individual may lose decision-making capacity before their preferred date of receiving MAID if their natural death is reasonably foreseeable
  - legislation in Canada continues to be under parliamentary review as new patient groups and circumstances are added
  - note: At this time, patients whose sole eligibility is a mental health diagnosis cannot access MAID. This is being reviewed with an expected date of March 2024

Canada's Medical Assistance in Dying (MAID) Law [Internet]. Canada: Government of Canada; [updated 2023 Jun 19; cited 2023 April 30]. Available from: https://www.justice.gc.ca/eng/cj-jp/ad-am/bk-di.html

Types of Grief

- anticipatory grief – feelings of grief occurring before an impending loss, including being concerned for the dying person, balancing conflicting demands, and preparing for death
- acute grief – immediate reaction to the death of a loved one. In the majority of cases, support from family and friends over time will help the bereaved accept the loss
- complicated grief – unanticipated progression of grief, which severely interferes with a person's ability to function. Characterized by prolonged duration, maladaptive thoughts, dysregulated emotions, and dysfunctional behaviours; depression and anxiety may be prevalent

Self-Care

Definition

- proactive, holistic pursuit of personal well-being in tandem with professional responsibility for patient well-being

Benefits

- balances compassion for oneself and compassion for others
- translates improvements in professionals' quality of life to improvements in patients' care
  - positively predicts competence in coping with death and achieving compassion satisfaction
  - negatively predicts risk of fatigue and burnout
- requires and cultivates self-awareness, i.e. the culmination of knowledge of and empathy for oneself
- promotes sustainable resilience through the development of coping skills, the balance between professional demands and personal needs, and the commitment to overall well-being

Strategies

- within the workplace: individual regulation of workload demands and establishment of boundaries, opportunity for team bonding/debriefing, promotion of resources/supports that can attend to professionals' needs, and development of a culture supportive of and conducive to self-care
- beyond the workplace: a range of health-promoting behaviours (e.g. balanced diet, sleep hygiene, exercise, meditation, interpersonal fulfillment, spiritual practice)

Pediatric Palliative Care

Unique Considerations for Pediatric Patients

- the unit of care in pediatric palliative care is always the family and the afflicted child. This includes siblings, who are often affected in various ways
- ideally should be offered early after diagnosing a potential life-limiting or life-threatening disease and continued through the course of treatment, along with standard/curative care
- respite services for families is a key aspect of palliative care for medically complex and technology-dependent children
- bereavement support to parents and siblings after the death of a child is a standard offering
  - emotional maturity and cognitive abilities vary between children and adults, and are determined by the developmental level of the child rather than their chronological age
  - unique pediatric life-threatening illnesses – less than 30% of patients referred to pediatric palliative care teams have cancer; the majority have congenital or acquired neurologic impairment, many of whom are technology-dependent

Predominant Pediatric Conditions Receiving Palliative Care:
1. Genetic/congenital disease (40.8%)
2. Neuromuscular disease (39.2%)
3. Cancer (19.8%)
4. Respiratory disease (12.8%)
5. Gastrointestinal disease (10.7%)

- unique challenge of dealing with the child, parents, and siblings
- decision-making authority, even in matters related to EOL, depends on the young person's capacity. However, many decisions are family-centered, and made with the pediatric patient and the parents together

Table 3. Categories of Pediatric Patients Who May Benefit From Palliative Care

Category 1	**Life-threatening conditions for which curative treatment may be feasible but can fail** Palliative care is involved when treatment fails or during acute crisis Palliative care is no longer required upon achieving long-term remission or successful treatment e.g. cancer, irreversible organ failure
Category 2	**Conditions in which premature death is inevitable** Intensive treatment over a long period of time to prolong life and allow normal activities e.g. cystic fibrosis, Duchenne muscular dystrophy
Category 3	**Progressive conditions without curative treatment options** Treatment is exclusively palliative and can extend over many years e.g. Batten disease
Category 4	**Irreversible but non-progressive conditions causing severe disability** e.g. severe cerebral palsy, multiple disabilities after brain or spinal cord injury

Source: A guide to children's palliative care: supporting babies, children and young people with life-limiting and life-threatening conditions and their families. Together for Short Lives 2018

Pediatric Palliative Care Patients: A Prospective Multicenter Cohort Study
Paediatrics 2011;127:1094-1101
Purpose: To describe the clinical characteristics and outcomes of patients who receive hospital-based pediatric palliative care (PPC) consultations.
Methods: Prospective cohort study of 515 patients in the United States and Canada from January to March 2008.
Results: The predominant primary clinical conditions were genetic/ congenital (40.8%), neuromuscular (39.2%), cancer (19.8%), respiratory (12.8%), and gastrointestinal (10.7%). During the 12-mo follow-up, 30.3% of the cohort died; the median time from consult to death was 107/d.
Conclusion: PPC serves a diverse cohort of children and young adults with life-threatening conditions. Most PPC patients are alive for more than 1 yr after initiating PPC.

Assessment Tools

Symptom Screening in Pediatrics Tool (SSPedi)
- used in children age 8-18 yr to assess symptoms over time and the efficacy of interventions
- symptoms rated on a five-point descriptive Likert scale
- assesses depression, anxiety, irritability, memory/cognition, changes in appearance, fatigue, mouth sores, headache, pain, tingling/numbness of extremities, N/V, appetite, changes in taste, constipation, and diarrhea

Mini-SSPedi
- a revised SSPedi geared towards children 4-7 yr
- assesses the same 15 symptoms
- uses a three-point, face-based Likert scale
- keep in mind the child's stage of development when interpreting these tools
  - children 4-5 yr can describe concrete aspects of their own health
  - introspection develops around ages 6-8 yr

Memorial Symptom Assessment Scale (MSAS)
- used in children 7+ yr
- measures frequency, severity, and distress associated with 32 common physical and psychological symptoms
- uses a five-point Likert scale
- used in both clinical and research settings

Symptom Management

- children are often aware of their condition, and open communication with the child in regard to diagnosis and prognosis is encouraged to reduce anxiety and fear
  - child's stage of development and cognitive abilities should be considered when discussing concepts of illness, treatment decisions, EOL, and dying
- symptoms encountered near EOL, and their respective management are similar to that in adult care (see *Table 2, PM4*). However, the following are unique in pediatric management:
  - shared decision making involving the child (to the extent possible or desired), the parents, and the healthcare providers typically guides treatment and EOL care
  - symptom management may be over the course of years and therefore may require a transition plan into adult palliative services
  - play therapy and unstructured play reduces anxiety, depression, and aggression
  - creating a sense of normality in the child's life aids in emotional wellbeing (e.g. seeing friends, attending school, parental discipline)
  - the patient's pain and anxiety often correlate with parental anxiety and quality of life, and therefore managing these symptoms benefits the family unit
  - siblings should also be offered psychological supports

Equity in Palliative Care

- healthy equity is the idea that everyone should be able to equally achieve their full health potential regardless of their background and social factors. Unfortunately, achieving this equity is still an ongoing issue. Some examples of health inequity include reduced primary and/or specialist care, lower life expectancy, and a larger number of preventable deaths due to factors including race, homelessness, socioeconomic status etc
- although palliative care is a vital component of healthcare with demonstrated improvements in quality of life, access to palliative care is not always equitable. Characteristics that can lead to poorer access to palliative care include:
  - older age
  - race
  - not married
  - living alone
  - non-cancer diagnoses
  - sexual/gender minority
  - homelessness
  - low socioeconomic status
  - living in a long term care centre (LTC)
  - lower caregiver educational attainment
  - residing in a rural area
  - presence of a physical or intellectual disability
  - immigrant status
- therefore, it is important to recognize these factors and account for our own biases, assumptions, and privileges to help provide competent, inclusive palliative care to patients from diverse backgrounds

Landmark Palliative Medicine Trials

Trial Name	Reference	Clinical Trial Details
PALLIATIVE APPROACH TO CARE		
Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer	NEJM 2010; 363:733-742	**Title**: Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer **Purpose**: To examine the effect of introducing early palliative care after diagnosis of metastatic non–small-cell lung cancer on patient-reported outcomes and end-of-life care. **Methods**: Patients (n=322) were randomized to receive either an early nurse-led palliative care intervention addressing physical and psychosocial needs in addition to usual oncologic care vs. routine oncology care. Primary outcomes included QoL, symptom intensity, and mood. **Results**: Of 151 randomized patients, 27 passed away, and 107 (86% of the remaining patients) completed assessments. Patients assigned to early palliative care had a better QoL, lower depressive symptoms, and longer median survival vs. standard care (11.6 mo vs. 8.9 mo, P=0.02). **Conclusions**: Early palliative care led to significant improvements in both QoL and mood among patients. Despite lesser aggressive EOL care, the intervention group had longer survival.
Early Palliative Care for Patients With Advanced Cancer	Lancet 2014 17;383(9930):1721-30	**Title**: Randomized Controlled Trial of Early Palliative Care for Patients With Advanced Cancer **Purpose**: To assess the impacts of early palliative care on patients with advanced cancer. **Methods**: RCT consisting of 461 patients who had advanced cancer, and a prognosis of 6-24 mo. Patients were randomized to receive consultation and follow-up by a palliative care team or to receive standard cancer care. The outcomes of interest were quality of life, assessed using Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-Sp) at 3 mo, and Quality of Life at the End of Life (QUAL-E) scale; symptom severity, assessed using Edmonton Symptom Assessment System (ESAS); and satisfaction with care, assessed using FAMCARE-P16. **Results**: Results show that there was no significant difference in the FACIT-Sp score at the primary endpoint and there was an improvement in quality of life by +2.25 points on the QUALE-scale within the treatment group compared to the control. There was also a significant difference in satisfaction with the quality of care by +3.79 points on the FAMCARE-P16 scale within the treatment group compared to the control. There was no significant difference in symptom severity. **Conclusions**: Although there was no change in quality of life at the primary endpoint, improvements in the QUAL-E and FAMCARE-P16 scores are promising and warrant further research.
COSMIC	Lancet 2022;399(10325):656-664	**Title**: Effectiveness of a three-step support strategy for relatives of patients dying in the intensive care unit **Purpose**: Evaluate the effectiveness of a proactive communication and support intervention involving physicians and nurses at reducing prolonged grief in relatives. **Methods**: RCT consisting of 875 relatives aged >18 yr who have made a decision to withdraw or withhold life support. Patients were randomized to receive standard of care support and communication, or a physician-driven, nurse-aided, three-step support strategy. The outcome of interest was the proportion of relatives with prolonged grief as indicated by a score ≥30 on the Prolonged Grief Scale (PG-13), 6 mo after the death. **Results**: A smaller proportion of relatives randomized to receive the involved communication strategy experienced prolonged grief (15%) when compared to the control group (21%). Associated PG-13 scores were also comparatively lower in the group that received the involved communication strategy. **Conclusions**: A physician-driven, nurse-aided, three-step support strategy is effective at reducing prolonged grief in relatives coping with the loss of a family member.

Trial Name	Reference	Clinical Trial Details
ENABLE II	JAMA 2009;302:741-749	**Title**: Effects of a Palliative Care Intervention on Clinical Outcomes in Patients with Advanced Cancer: the Project ENABLE II Randomized Controlled Trial **Purpose**: To determine the effect of a nursing-led intervention on QoL, symptom intensity, mood, and use of resources in patients with advanced cancer. **Methods**: Patients were randomized to receive multi-component intervention vs. usual care (n=322). Intervention included telephone-based care by advanced palliative care trained nurses, who provide structured educational and problem-solving sessions, to encourage patient activation, self-management, empowerment and follow-up at least monthly with every patient. Primary outcomes included QoL, symptom intensity, and mood. Intensity of service was measured using days in the hospital and number of ED visits. **Results**: Longitudinal intention-to-treat analyses for the total sample revealed higher QoL, lower depressed mood, and a trend toward lower symptom intensity. Similar results were seen among patients who passed away, except there was no change in symptom intensity. No differences were noted in the number of days in the hospital, ICU, or ED visits. **Conclusions**: A nurse-led, palliative care-focused intervention addressing physical and psychosocial care along with oncology care improved scores for QoL and mood.
ENABLE III	J Clin Oncol 2015 1;33(13):1438-45	**Title**: Early vs. Delayed Initiation of Concurrent Palliative Oncology Care **Purpose**: To determine the impact of early vs. delayed initiation of concurrent palliative oncology care on mood, symptom impact, quality of life, and 1-yr survival rate. **Methods**: RCT consisting of 207 patients with advanced cancer. Patients were randomized to receive in-person palliative care (PC) consultation, structured PC telehealth nurse coaching sessions, and monthly follow-ups upon admission or within 3 mo of admission. The outcomes of interest were quality of life, symptom impact, mood, 1-yr survival, hospital/intensive care unit days, emergency room visits, chemotherapy in the last 14 d, and death location. **Results**: Mood and quality of life were not significantly different between the two groups. 1-yr survival rates were greater in the early intervention compared to the delayed intervention. Relative rates of hospital days, ICU days, emergency room visits, and chemotherapy in the last 14 d of life were similar between the two groups. **Conclusions**: Although, self-reported outcomes, and resource use were not significantly different between the two groups, there was an improvement in 1-yr survival rates.
Effect of Palliative Oxygen Versus Room Air in Relief of Breathlessness in Patients with Refractory Dyspnea	Lancet 2010;376:784-793	**Title**: Effect of Palliative Oxygen Versus Room Air in Relief of Breathlessness in Patients with Refractory Dyspnea: A Double-blind, Randomized Controlled Trial **Purpose**: To determine the effectiveness of oxygen compared with room air for relief of breathlessness in individuals with a life-limiting illness who were ineligible for long-term oxygen therapy. **Methods**: Eligible participants (n=239) were randomly assigned to receive oxygen or room air through a nasal cannula at 2 L per min for 7 d, for at least 15 h per day. Breathlessness (10 pt. scale) was measured twice daily. **Results**: Mean morning breathlessness changed by -0.9 points (95% CI -1.3 to -0.5) in the oxygen group and by -0.7 points (-1.2 to -0.2) in the room air group. Mean evening breathlessness changed by -0.3 points (-0.7 to 0.1) in the oxygen group and by -0.5 (-0.9 to -0.1) in the room air group (P=0.554). Frequency of side effects did not differ between groups. **Conclusion**: Oxygen delivery by nasal cannula provides no additional symptomatic benefit for relief of refractory dyspnea compared to room air.
Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness	JAMA Intern Med 2015;175(5):691-700	**Title**: Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness: A Randomized Clinical Trial **Purpose**: To evaluate the safety, clinical impact, and cost of discontinuing station medications for patients in the palliative care setting. **Methods**: Patients (n=389) with a life expectancy between 1 mo to 1 yr and on statin therapy for 3 mo were randomized to either discontinue or continue statin therapy with monthly monitoring for up to 1 yr. **Results**: The proportion of patients in the discontinuation vs. continuation groups who died within 60 days was not significantly different (23.8% vs. 20.3%, P=0.36). For the discontinuation group, total quality of life was better (P=0.03), few patients experienced CVD events (13 vs. 11) and mean cost savings were $716 per patient. **Conclusions**: Stopping statin medication therapy is safe and may be associated with improved quality of life and a reduction in medication costs.
PATIENT ASSESSMENT		
Comprehensive Discharge Planning and Home Follow-up of Hospitalized Elders: A Randomized Clinical Trial	BMJ 2000;320:469	**Title**: Extent and Determinants of Error in Doctors' Prognoses in Terminally Ill Patients: Prospective Cohort Study **Purpose**: To describe doctors' prognostic accuracy in terminally ill patients and to evaluate the determinants of that accuracy. **Methods**: Prospective cohort study involving 343 doctors who provided survival estimates for 468 terminally ill patients at the time of hospice referral. Main outcome measures were the estimated and actual survival of patients. **Results**: Median survival was 24 d. Only 20% (92/468) of predictions were accurate (within 33% of actual survival); 63% (295/468) were overly optimistic and 17% (81/468) were overly pessimistic. Overall, doctors overestimated survival by a factor of 5.3. **Conclusions**: Doctors are systematically optimistic in estimating prognosis for terminally ill patients. This phenomenon may adversely affect the quality of care given to patients near the EOL.

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P Pediatrics

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Acronyms

AAP American Academy of Pediatrics
ABC airway, breathing, circulation
ABG arterial blood gas
ACE angiotensin converting enzyme
ACEI angiotensin converting enzyme inhibitor
ADH antidiuretic hormone
AGA appropriate for gestational age
ALL acute lymphoblastic leukemia
ALP alkaline phosphatase
ALPS autoimmune lymphoproliferative syndrome
ALT alanine transaminase
AML acute myelogenous leukemia
ANA antinuclear antibody
ANCA anti-neutrophil cytoplasmic antibody
AOM acute otitis media
ARB angiotensin receptor blocker
ARBD alcohol-related birth defects
ARND alcohol-related neurodevelopmental disorder
ASA acetylsalicylic acid
ASD atrial septal defect
ASOT antistreptolysin-o titre
AST aspartate aminotransferase
ATN acute tubular necrosis
AVM arteriovenous malformation
BRUE brief resolved unexplained events
BUN blood urea nitrogen
C&S culture and sensitivity
CAH congenital adrenal hyperplasia
CAS Children's Aid Society
CBC complete blood count
CDGP constitutional delay of growth and puberty
CF cystic fibrosis
CFTR cystic fibrosis transmembrane conductance regulator
CHD congenital heart defect
CHF congestive heart failure
CK creatine kinase
CML chronic myelogenous leukemia
CMV cytomegalovirus
COPD chronic obstructive pulmonary disease
CP cerebral palsy
CPAP continuous positive airway pressure
CPS Canadian Pediatric Society
Cr creatinine
CRP C-reactive protein
DAT direct antiglobulin test
DDAVP 1-desamino-8-D-arginine vasopressin
DI diabetes insipidus
DIC disseminated intravascular coagulation
DKA diabetic ketoacidosis
DM diabetes mellitus
DMARD disease modifying antirheumatic drug
DS Down syndrome
DSD disorder of sexual differentiation
EBV Epstein-Barr virus
Echo echocardiogram
ESR erythrocyte sedimentation rate
FAS fetal alcohol syndrome
FASD fetal alcohol spectrum disorder
FISH fluorescent in situ hybridization
FSS familial short stature
FTT failure to thrive
G6PD glucose-6-phosphate dehydrogenase
GA gestational age
GAS group A Streptococcus
GBM glomerular basement membrane
GBS group B Streptococcus
GERD gastroesophageal reflux disease
GFR glomerular filtration rate
GN glomerulonephritis
GSD glycogen storage disease
GTPAL Gravidity Term Preterm Abortion Living
HBsAg hepatitis B surface antigen
HDNB hemorrhagic disease of the newborn
HEEADSSS Home Education/Employment Eating Activities Drugs Sexuality Suicide/depression Safety/violence
Hib Haemophilus influenzae type b
HIDA hepatobiliary iminodiacetic acid
HIE hypoxic ischemic encephalopathy
HLA human leukocyte antigen
HPA human platelet antigen
HRV human rotavirus
HSP Henoch-Schönlein purpura
HSV herpes simplex virus
HTN hypertension
HUS hemolytic uremic syndrome
IBD inflammatory bowel disease
IBS irritable bowel syndrome
IBW ideal body weight
ICH intracranial hemorrhage
ICP intracranial pressure
IL interleukin
INR international normalized ratio
ITP immune thrombocytopenic purpura
IUGR intrauterine growth restriction
IVH intraventricular hemorrhage
IVIg intravenous immunoglobulin
JIA juvenile idiopathic arthritis
LAH left atrial hypertrophy
LBW low birth weight
LGA large for gestational age
LLSB lower left sternal border
LMN lower motor neuron
LOC level of consciousness
LP lumbar puncture
LRTI lower respiratory tract infection
LV left ventricle
LVH left ventricular hypertrophy
MAS meconium aspiration syndrome
MCAD medium-chain acyl-CoA dehydrogenase
MCD minimal change disease
MDI metered dose inhaler
MEE middle ear effusion
MSUD maple syrup urine disease
NAD nicotine adenine dinucleotide
NCS nerve conduction study
NEC necrotizing enterocolitis
NF neurofibromatosis
NG nasogastric
NICU neonatal intensive care unit
NP nasopharyngeal
NPO nothing by mouth
NS normal saline
OCP oral contraceptive pill
OME otitis media with effusion
ORT oral rehydration therapy
OSA obstructive sleep apnea
OT occupational therapy
PAC premature atrial contraction
PCOS polycystic ovarian syndrome
PDA patent ductus arteriosus
PE pulmonary embolism
PKU phenylketonuria
PO by mouth
PPHN persistent pulmonary hypertension of newborn
PPV positive pressure ventilation
PT physiotherapy
PTH parathyroid hormone
PTT partial thromboplastin time
PUVA psoralen + UVA
RAD right axis deviation
RAS renal artery stenosis
RBBB right bundle branch block
RDS respiratory distress syndrome
RF rheumatoid factor
Rh Rhesus factor
RL Ringer's lactate
ROM range of motion
RSV respiratory syncytial virus
RUSB right upper sternal border
RVH right ventricular hypertrophy
RVOTO right ventricular outflow tract obstruction
SEM systolic ejection murmur
SGA small for gestational age
SIADH syndrome of inappropriate antidiuretic hormone
SIDS sudden infant death syndrome
SLE systemic lupus erythematosus
STEC Shiga toxin-producing E. coli
SVT supraventricular tachycardia
TB tuberculosis
TEF tracheoesophageal fistula
TM tympanic membrane
TMJ temporomandibular muscle and joint
TNF tumour necrosis factor
TPN total parenteral nutrition
TTN transient tachypnea of the newborn
UMN upper motor neuron
URTI upper respiratory tract infection
UVA ultraviolet A
VCUG voiding cystourethrogram
VKDB vitamin K deficiency bleeding
VSD ventricular septal defect
VUR vesicoureteral reflux
WPW Wolff-Parkinson-White

Pediatric Quick Reference Values

Table 1. Normal HR and RR at Various Ages

Age (yr)	Awake Pulse (bpm)	Asleep Pulse (bpm)	Respiratory Rate (br/min)
Neonate (<28 d)	100-205	90-160	30-53
Infant (1-12 mo)	100-190	90-160	30-53
Toddler (1-2 yr)	98-140	80-120	22-37
Preschool (3-5 yr)	80-120	65-100	20-28
School-age (6-11 yr)	75-118	58-90	18-25
Adolescent (12-15 yr)	60-100	50-90	12-20

Table 2. Normal sBP at Various Ages

Age	sBP (mmHg)
Birth <1 kg (12 h)	39-59
Birth 3 kg (12 h)	60-76
Neonate (96 h)	67-84
Infant (1-12 mo)	72-104
Toddler (1-2 yr)	86-106
Preschool (3-5 yr)	89-112
School-age (6-9 yr)	97-115
Preadolescent (10-11 yr)	102-120
Adolescent (12-15 yr)	110-131

Table 3. Normal Temperature Ranges

Method	Normal Temperature Range	Fever
Rectal	36.6°C to 38°C	≥38°C
Ear	35.8°C to 38°C	≥38°C
Oral	35.5°C to 37.5°C	≥37.5°C
Axillary	36.5°C to 37.5°C	≥37.5°C

Canadian Immunization Guide
National Advisory Committee on Immunization. Canadian Immunization Guide (CIG). Last Modified 2021. Public Health Agency of Canada, 2006. Available at: https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html

Table 4. Temperature Measurement Technique Recommendations

Age	Suggested Technique
Birth to 2 yr	1. Rectal (definitive) 2. Axillary (screening low risk children)
Over 2 yr to 5 yr	1. Rectal (definitive) 2. Axillary, Tympanic (or Temporal Artery if in hospital) (screening)
Older than 5 yr	1. Oral (definitive) 2. Axillary, Tympanic (or Temporal Artery if in hospital) (screening)

Primary Care

Visit Overview

- schedule of well-child visits
  - newborn (within 48-72 h post-discharge), 2, 4, 6, 9, 12, and 18 mo
  - annually between ages 2-5; every 1-2 yr between ages 6-18 (annual recommended)
- content
  - history and physical exam including growth, development/school, sleep, screening (dental, vision), and nutrition
  - social history (HEEADSSS or SSHADESS for adolescents)
  - routine immunizations
  - counselling and anticipatory guidance
  - see evidence based clinical tools such as Rourke Baby Record (birth - age 5) and Greig Health Record (age 6 - 17) for more information

Standard Pediatric History

- **BINDS: B**irth, **I**mmunization, **N**utritional, **D**evelopmental, **S**ocial
- ID: name, age, sex, gender identity, major chronic medical concerns
- chief complaint (CC)/reason for referral (RFR)
- HPI: child and caregiver
  - OPQRSTU
  - recent travel, sick contacts
- obstetrical history (for newborns and infants)
  - prenatal/pregnancy history
    - conception
    - GTPAL
    - screening: blood group, antibody screen, Rh, DAT, HBsAg, rubella, syphilis, HIV, GBS
    - genetic screening: maternal serum screening (MSS), first trimester screening (FTS), integrated prenatal screening (IPS), amniocentesis, special tests
    - ultrasounds
    - **complications**: illnesses, infections, bleeding, gestational diabetes (GDM), gestational hypertension (GHTN)
    - medications, vitamins, iron, fetal exposure to smoking, alcohol, other substances
    - maternal mental health screen
  - labour and delivery history
    - **labour complications**: prolonged rupture of membranes, maternal fever, fetal tachycardia, meconium
    - type of delivery: spontaneous vaginal delivery, interventions required: forceps, vacuum, caesarean delivery (CD)
    - medications used during labour
  - neonatal history
    - gestational age at birth
    - birth weight, head circumference, length (%iles)
    - resuscitation: APGARs
    - length of hospital stay, NICU stay
    - neonatal complications: prematurity, respiratory distress, jaundice, infection, seizures, hypoglycemia
- past medical history
  - hospitalizations, ED visits, past surgeries, chronic illnesses, accidents or injuries, community resources/services involved or referrals in place, other specialists involved in care
- medications (including vitamins/supplements)
- allergies (food and medication)
- immunizations (including contraindications, such as previous anaphylaxis, or immunosuppression)
- developmental history
  - review milestones
  - behavioural concerns
  - school / educational concerns
- nutritional history
  - infants: breast vs. formula feeding
  - cow's milk intake (max 16-24 oz)
  - solids, variety, etc.
  - iron rich foods
  - food insecurity

According to the Centers for Disease Control and Prevention (CDC), the weight of currently available scientific evidence does not support the hypothesis that the Measles, Mumps and Rubella (MMR) vaccine causes either autism or IBD. The landmark paper linking autism to the MMR vaccine (Lancet 1998;351:637-641) was retracted due to false claims in the article (Lancet 2010;375:445)

Adverse Reactions Associated with Any Vaccine
Local: induration, tenderness, redness, swelling
Systemic: fever, rash, irritability
Allergic: urticaria, rhinitis, anaphylaxis

Contraindication:
Moderate/severe illness ± fever
Allergy to vaccine component
No need to delay vaccination for mild URTI

Vaccination in Cases of Asplenia or Hyposplenia (such as Sickle Cell Disease)
- Should receive all routine immunizations, including the yearly influenza vaccine
- No vaccines are contraindicated, though live vaccines can be contraindicated in immunodeficiencies such as DiGeorge syndrome (22q11.2 deletion)
- Susceptible to infection by encapsulated bacteria ("SHiNE KISS" –*S. pneumoniae*, *H. influenzae*, *N. meningitidis*, *E. coli*, *Klebsiella*, *Salmonella*, Group B Strep), so must add:
  - Quadrivalent conjugated Meningococcal C vaccine (Men-C-ACYW) and Meningococcal B vaccine (4CMenB) at time of diagnosis if ≥2 mo (2-4 doses given at least 8 wk apart) with booster every 5 yr thereafter
  - Can omit routine Meningococcal-C-Conjugate at 12 mo if received Men-C-ACYW and expected to receive a second dose within 8 wk
  - Pneumococcal polysaccharide vaccine (Pneu-P-23) at ≥2 yr and single booster ≥5 yr after first dose
- Pneumococcal conjugate vaccine (Pneu-C-13) 1-2 doses 8 wk apart if ≥12 mo at time of diagnosis
  - Consider single booster Hib at >5 yr

- family history
  - consanguinity, recurrent pregnancy losses, early childhood deaths
- social history
  - who lives at home? Siblings?
  - does the child attend daycare or school? Primary caregivers?
  - school adjustment, friends, activities, safety, stability, stressors
  - HEEADSSS or SSHADESS history for adolescents
  - ITHELPS – income, transportation, home, education, legal status, personal safety, support

Routine Immunization

Table 5. Publicly Funded Immunization Schedule for Ontario

	DTaP-IPV-Hib	TdaP-IPV	Pneu-C-13	Rot-1	Men-C-C	MMR	Var	MMRV	Men-C-ACYW	HepB	HPV-9	Tdap	Inf	COVID-19
2 mo	√IM		√IM	√PO (up to 15 wk)										
4 mo	√IM		√IM	√PO (up to 32 wk)										
6 mo	√IM													√IM 2-3 doses** (6 mo - 4 yr)
12 mo			√IM		√IM	√SC								
15 mo							√SC							
18 mo	√IM													
4-6 yr*		√IM						√SC						√IM 2 doses + booster (≥ 5 yr)
Grade 7									√IM	√IM 2 doses (0,4-6 mo)	√IM 2 doses (0,6 mo)			
14-16 yr												√IM		
Every autumn (beginning at age 6 mo)													√IM	

IM = intramuscular; PO = per oral; SC = subcutaneous
* Preferably given at 4 yr of age
** Depends on COVID-19 vaccine brand
DTaP-IPV-Hib = diphtheria, tetanus, acellular pertussis, inactivated polio, Haemophilus influenzae type b vaccine (i.e. Pediacel®); TdaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (i.e. Adacel®-Polio); HepB = hepatitis B vaccine; HPV-9 = human papillomavirus vaccine; Inf = influenza vaccine; MMR = measles, mumps, rubella vaccine; Men-C-C = meningococcal conjugate c vaccine; Men-C-ACYW = meningococcal conjugate ACYW-135 vaccine; MMRV = measles, mumps, rubella, varicella vaccine; Pneu-C-13 = pneumococcal 13-valent conjugate vaccine; Rot-1 = rotavirus oral vaccine; Var = varicella vaccine; COVID-19 = coronavirus vaccine

Table 6. Adverse Reactions and Contraindications of Routine Immunizations

Vaccine	Adverse Reaction	Contraindication
TdaP-IPV	Prolonged crying Hypotonic unresponsive state (rare) Seizure on day of vaccine (rare)	Evolving unstable neurologic disease Hyporesponsive/hypotonic following previous vaccine Anaphylactic reaction to TdaP-IPV vaccine or its components (e.g. neomycin or streptomycin) in the past History of encephalopathy within 7 d of past pertussis vaccine, history of GBS within 8 wk of past tetanus vaccine
Rot-1	Cough Diarrhea, vomiting Fever Intussusception	History of intussusception Immunocompromised Abdominal disorder (e.g. Meckel's diverticulum)
MMR	Measles-like rash (7-14 d) Lymphadenopathy, arthralgia, arthritis Parotitis (rare) Especially painful injection Transient thrombocytopenia (1/30000)	Pregnancy Immunocompromised infants (except healthy HIV positive children) Anaphylactic reaction to gelatin Cannot give MMR within 4 wk of TB skin test, but can receive on same day
Var	Mild varicella-like papules or vesicles; 2 wk may get local or generalized rash	Pregnant or planning to get pregnant within 3 mo Anaphylactic reaction to Var vaccine or its components (e.g. gelatin) in the past
HepB		Anaphylactic reaction to vaccine components (e.g. Baker's yeast)
MMRV	Same as MMR and Var vaccines	Same as MMR and Var vaccines
DTaP		1st trimester pregnancy
Inf	Malaise, myalgia Febrile seizure when given with Pneu-C-13 or DTaP Hypersensitivity reaction	<6 mo of age Immunocompromised Egg-allergic individuals – Live attenuated influenza vaccine is not recommended for those with an egg allergy. In these individuals, trivalent or quadrivalent vaccine can be given in an environment where anaphylaxis can be managed

* Currently only publicly funded for select groups (asplenia, antibody/complement deficiencies, cochlear implant recipients, HIV, close contacts with infected individuals)
DTaP = diphtheria, tetanus, acellular pertussis vaccine; TdaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (i.e. Adacel®-Polio); HepB = hepatitis B vaccine; HPV-9 = human papillomavirus vaccine; Inf = influenza vaccine; MMR = measles, mumps, rubella vaccine; Men-B = multicomponent meningococcal B vaccine; Men-C-C = meningococcal conjugate c vaccine; Men-C-ACYW = meningococcal conjugate ACYW-135 vaccine;
MMRV = measles, mumps, rubella, varicella vaccine; Rot-1 5 = rotavirus oral vaccine; Var = varicella vaccine; COVID-19 = coronavirus vaccine

Injection site
Infants (<12 mo): anterolateral thigh

A Systematic Review of the Effect of Rotavirus Vaccination on Diarrhea Outcomes Among Children Younger Than 5 Years
Pediatr Infect Dis J 2016;35(9):992-998
Purpose: To review evidence of rotavirus vaccine efficacy and effectiveness by Millennium Development Goal Region.
Method: RCTs and observational studies on rotavirus vaccine in children <5 y/o were included in this review. Primary outcomes included rotavirus diarrhea or diarrhea of unspecified etiology. Secondary outcomes included diarrhea episodes of any severity, and severe diarrhea episodes, hospitalization, and death.
Results: 48 studies were eligible for inclusion in this review. Rotavirus vaccine was found to be effective and efficacious. Across all millennium development regions rotavirus vaccine prevented rotavirus diarrhea, severe rotavirus diarrhea, and rotavirus hospitalization. The vaccine also reduced severe diarrhea and diarrhea related hospitalization in general.

Table 6. Adverse Reactions and Contraindications of Routine Immunizations

Vaccine	Adverse Reaction	Contraindication
HPV-9	Pruritus	Anaphylactic reaction to HPV-9 vaccine in the past
Men-B*		Anaphylactic reaction to Men-B vaccine or its components in the past
Men-C-ACYW	Syncope (rare)	Anaphylactic reaction to Men vaccine or its components in the past
COVID-19	Fatigue Headache Myalgia, arthralgia Chills	Thrombosis with thrombocytopenia syndrome to viral vector COVID-19 vaccine History of capillary leak syndrome

* Currently only publicly funded for select groups (asplenia, antibody/complement deficiencies, cochlear implant recipients, HIV, close contacts with infected individuals)
DTaP = diphtheria, tetanus, acellular pertussis vaccine; TdaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (i.e. Adacel®-Polio); HepB = hepatitis B vaccine; HPV-9 = human papillomavirus vaccine; Inf = influenza vaccine; MMR = measles, mumps, rubella vaccine; Men-B = multicomponent meningococcal B vaccine; Men-C-C = meningococcal conjugate c vaccine; Men-C-ACYW = meningococcal conjugate ACYW-135 vaccine;
MMRV = measles, mumps, rubella, varicella vaccine; Rot-1 5 = rotavirus oral vaccine; Var = varicella vaccine; COVID-19 = coronavirus vaccine

- adverse effects following immunization: must be reported to the local or regional health unit when the event: has a temporal association with a vaccine, has no other clear cause at the time of reporting, meets one or more of the seriousness criteria, is unexpected
- temperature regulation in vaccine storage: cold chain generally +2 to +8°C

Modifications to the Routine Vaccination Schedule

- catch-up immunization schedules for children not previously immunized or missing vaccine records (ie. newcomers)
- additional immunizations for children at-risk due to underlying medical conditions (ie. PCV23 for patients with asplenia, sickle cell disease)
- update Dec 2020: current Ontario catch-up program for HPV vaccine - 2-3 doses for Grades 8-11 (males) and Grades 8-12 (females)

Immunization of Immunocompromised Patients

- susceptibility to infection and vaccine response varies
- individualized vaccine schedule based on patient's immune status
- inactivated vaccines: may be administered if indicated; responses may be reduced or absent and duration of immunity may be reduced (compared to healthy individuals); dose increase or extra booster doses may be indicated
- live attenuated vaccines:
  - avoid if severely immunocompromised or if uncertain of immune status
  - can be given to those with isolated IgA, IgG subclass or complement deficiency, or asplenia
  - live viral vaccines are okay for most children with phagocyte or neutrophil disorders, but live bacterial vaccines are contraindicated
- additional vaccines: may need vaccines that are not usually recommended for otherwise healthy children or not usually administered beyond a certain age
- timing: vaccines should be administered when maximum immune response is expected (i.e. when not immunosuppressed medically, pharmacologically, or immediately post transplant)
- response: as immune response may be inadequate, consider post-immunization antibody titres if appropriate; positive serologic test may be due to immunoglobulin therapy or maternal antibody (infants <18 mo)

Vaccine-Hesitant Parents

- healthcare professional vaccine advice plays a key role in parental decision-making
  - do not dismiss vaccine-hesitant families from your practice
- use a presumptive approach (for giving the vaccine) and motivational interviewing
  - use open-ended questions and listen to parent concerns and opinions - do not assume the health concerns of the parent
  - address concerns non-judgmentally and non-confrontationally; validate why parents may hold their belief
  - use compelling stories of vaccine-preventable disease
- communicate clearly to discuss disease risks and vaccine benefits and risks
- address immunization pain and discuss options for pain reduction (e.g. breastfeeding, rub/stroke the skin near injection site, distraction techniques)
- community protection (herd immunity)
  - "wait and see" approach to vaccinate in an outbreak scenario is not advisable
  - promote altruism - not receiving immunization can have consequences for others
- parents who refuse to immunize their children need to be informed of associated risks of diseases and responsibilities - considerations include:
  - protection of child from acquiring illnesses (e.g. vaccine, avoid sick contacts)
  - not vaccinating risks the health of others (weakened immune system, chronic conditions, newborns, elderly)
  - inform healthcare professionals of lack of vaccination when child is sick
  - if a vaccine-preventable disease is in your community: get vaccine, may be required to stay away from school, consider disease-specific risks, learn what symptoms to look out for
  - tetanus (>10% mortality) does not have community protection
  - travel - vaccines specific to geographical regions, refused permission to travel

Growth and Development

Growth*

- growth is not linear
  - most rapid growth during first 2 yr and at puberty
- measurement of growth
  - WHO Growth Charts used to monitor growth in infants and children
  - premature infants (<37 wk) use Fenton Curve to assess for small for gestational age (SGA) vs. large for gestational age (LGA); corrected GA until 2 yr
  - body proportion = upper/lower segment ratio (use symphysis pubis as midpoint)
    - newborn = 1.7, adult male = 0.9, adult female = 1.0

Average Growth Parameters

Table 7. Parameters of Average Growth at Birth

	Normal	Growth	Comments
Birth Weight	3.25 kg (7 lbs)*	Gain 20-30 g/d (term neonate) 2 x birth wt by 4-5 mo 3 x birth wt by 1 yr 4 x birth wt by 2 yr	Weight loss (up to 10% of birth weight) in first 7 d of life is normal Neonate should regain birth weight by ~10-14 d
Length/Height	50 cm (20 in)*	25 cm in 1st yr 12 cm in 2nd yr 8 cm in 3rd yr, then 4-7 cm/yr until puberty 8-12 cm/yr in adolescence 1/2 adult height at 2 yr	Measure supine length until 2 yr, then measure standing height
Head Circumference	35 cm (14 in)*	2 cm/mo for 1st 3 mo 1 cm/mo at 3-6 mo 0.5 cm/mo at 6-12 mo	Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference

* note these are averages, and may differ based on ethnicity and gestational age

Reflexes

Table 8. Developmental or Primitive Reflexes

Reflex	Manoeuver to Elicit Reflex	Appropriate Reflex Response	Age of Disappearance
Moro	Infant placed semi-upright, head supported by examiner's hand, sudden withdrawal of supported head with immediate return of support	Abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms	3-6 mo
Galant	Infant held in ventral suspension and one side of back is stroked along paravertebral line	Pelvis will move in the direction of stimulated side	2-3 mo
Grasp	Placement of examiner's finger in infant's palm	Flexion of infant's fingers	3-4 mo
ATNR	Turn infant's head to one side	"Fencing" posture (extension of ipsilateral arm and leg, flexion of contralateral arm and leg)	4-6 mo
Stepping	Dorsal surface of infant's foot placed touching edge of table	Flexion followed by extension of ipsilateral limb up onto table (resembles primitive walking)	2-3 mo
Rooting	Stroke infant's cheek	Infant turns head and opens mouth to suck on same side that cheek was stroked	2-3 mo
Lateral Propping	Tilt infant to side while in sitting position	Ipsilateral arm extension, present by 6-8 mo	Does not disappear

ATNR = asymmetric tonic neck reflex

Abnormal Reflex Response (primitive reflex response present in infancy; tendon reflex response always present)

Primitive reflex responses are abnormal if: absent during neonatal period; asymmetric; or persistent after 4-6 mo (e.g. cerebral palsy)

Tendon reflex responses: asymmetry suggests focal motor lesions (e.g. brachial plexus injury) and absence or hyper-reflexia may suggest CNS abnormality

Upgoing plantar reflex (Babinski's sign) normal in infants up to 2 yr

Developmental Milestones

Table 9. Developmental Milestones

Age*	Gross Motor	Fine Motor	Speech and Language	Cognitive/ Problem Solving	Social/Emotional
Newborn	Primitive reflexes: step, place, Moro, Babinski, ATNR; flexed posture	Primitive reflex: grasp	Primitive reflexes: root, suck; orients to sound; variable cries	Fixes and follows slow horizontal arc; prefers contrast, colours, faces, high-pitched voices; visual focal length ~10"	Bonding between parent and child
2 mo	Raises head 45° when prone	Hands open half the time, bats at objects	Turns to voice, cooing	Prefers familiar caregiver	Social smile
4 mo	Rolls prone to supine, sits with support, raises head up 90° and lifts chest when prone	Palmar grasp, reaches and obtains items, brings objects to midline	Squeals, laughs	Purposeful sensory exploration of objects (eyes, hands, mouth), anticipates routines	Explores parent's face
6 mo	Tripod sit, rolls both ways, postural reflexes	Transfers objects from hand to hand, raking grasp	Babbles (nonspecific)	Stranger anxiety, looks for dropped object	Expresses emotions: happy, sad, mad; memory for ~24 hr
9 mo	Sits well without support, crawls (not all), pulls to stand	Inferior pincer grasp, pokes objects	"Mama, dada" Gestures "bye bye", "up", gesture games	Plays games (e.g. peek-a-boo) Object permanence	Separation anxiety
12 mo	Walks a few steps, wide gait	Fine pincer (fingertips), finger-feeds cheerios, voluntary release	1 word with meaning (besides mama, dada), responds to own name, follows 1-step command with gesture	Uses objects functionally, cause and effect, trial and error, imitates	Points at wanted items, narrative memory
15 mo	Walks without support, crawls up stairs/steps	Stacks 2 blocks, uses spoon	4-5 words, follows 1-step command without gesture, 1 body part	Looks for moved hidden object if saw it being moved	Shared attention: points at interesting items to show to parent
18 mo	Runs, stoops and recovers	Tower of 4 blocks, scribbling, fisted pencil grasp, removes clothing	15-25 words 3 body parts	Symbolic play with doll or bear	Parallel play
24 mo	Jumps on two feet, up and down stairs 'marking time'	Tower of 6 blocks, handedness established, uses utensil	2-3 word phrases, uses "I, me, you," 50% intelligible, understands 2-step commands, 50+ words	New problem-solving strategies without rehearsal	Testing limits, tantrums, negativism ("no!"), possessive ("mine!")
3 yr	Rides tricycle, climbs up stairs alternating feet	Toilet trained, undresses, draws circle and cross (+)	3-step commands, 3-4 word phrases, "W" questions ("why?"), 200 words, 75% intelligible	Identifies shapes, counts to 3, simple time concepts	Cooperative play, role play (pretend play), separates easily, sharing
4 yr	Hops on 1 foot, climbs down stairs 1 foot per step	Uses scissors, buttons clothes	Speech 100% intelligible, uses past tense, tells a story	Identifies 4 colours, counts to 4	Has a preferred friend, elaborate fantasy play
5 yr	Skips, rides bicycle	Prints name, ties shoelaces, tripod pencil grasp	Fluent speech, future tense	Counts to 10 accurately, recites ABCs	Has group of friends

*If premature, use corrected GA until 2 yr

Developmental Red Flags

Gross motor: not walking at 18 mo; rolling too early at <3 mo

Fine motor: hand preference at <18 mo

Speech: <6 words at 18 mo

Social: not smiling at 4 mo; not pointing at 15-18 mo

See the Nipissing District Developmental Screen for a checklist of important 18 mo milestones: www.ndds.ca

Regression (i.e. loss of a previously acquired skill) is a red flag at any age

See Landmark Pediatric Trials table for more information on LEAP trial, which details the benefits of early introduction of peanuts in decreasing prevalence of peanut allergies in children deemed at risk.

See Landmark Pediatric Trials table for more information on the IMPACT trial, which assesses the efficacy and safety of oral immunotherapy in children with peanut allergy.

Dietary Exposures and Allergy Prevention in High-Risk Infants
Pediatr Child Health 2021;26(8):504-505
For infants at high risk of food allergy (personal history of atopy or a first-degree relative with an atopic condition), there is compelling evidence that the introduction of allergenic foods (e.g. cooked egg, peanut) at about 6 mo (but not before 4 mo of age) can help to prevent common food allergies. For low-risk infants, allergenic foods can be introduced around 6 mo of age. There is insufficient evidence to recommend vitamin D, omega 3, or pre- or probiotic supplements to prevent food allergies in infants. There is insufficient evidence to recommend modifying maternal diet to prevent food allergy. Breastfeeding is encouraged regardless of issues pertaining to food allergy prevention.

Nutrition

Dietary Requirements

Weight	<10 kg	10-20 kg	>20 kg
Needs	100 kcal/kg/d	1000 cal + 50 kcal/kg/d for each kg >10	1500 cal + 20 kcal/kg/d for each kg >20

Dietary Recommendations

- 0-6 mo: breast milk or formula
  - exclusive breastfeeding during first 6 mo is recommended unless contraindicated; breastfeeding until age 2 yr is beneficial; can continue as long as mother and child want
  - all breastfed infants require vitamin D supplement (400 IU/d or 800 IU/d if infant or maternal risk factors present)
- 4-6 mo: solid food introduction – do not delay beyond 9 mo for oral motor development
  - 2-3 new foods per wk, wait at least 2 d in between each food to allow time for adverse reaction identification

- early introduction of highly allergenic foods is recommended
- common allergenic foods: eggs, milk, mustard, peanuts, seafood, sesame, soy, tree nut, wheat
- initiate solids with iron-fortified cereals, meats, meat alternatives as iron stores at nadir at 6 months of age
- progress food textures from consistent smooth puree to gradually offering lumpy, soft-cooked, pureed, mashed textured foods
- encourage self-feeding and introduce open cup (should be done by 12 mo)

•9-12 mo: switch to homogenized (3.25%) cow's milk, maximum 16 oz/d by cup
- offer iron rich foods, vegetables, fruit, grains first; then milk or water
- provide up to 3 meals with 1-2 snacks daily at set times in high chair without distractions
- foods to avoid
  - honey until past 12 mo (risk of botulism)
  - added sugar, salt
  - excessive milk (i.e. maximum 500 mL or 16 oz/d after 1 yr) - associated with iron deficiency anemia
  - recommend no juice intake (high sugar)
  - anything that is a choking hazard (chunks, hard candies, nuts, round foods like grapes, hot dogs)

•12-24 mo: discontinue bottles

Breastfeeding

•content of breast milk
- colostrum (first few days postpartum): clear, rich in nutrients (i.e. high protein, low fat), immunoglobulins
- mature milk: 70:30 whey:casein ratio, fat from dietary butterfat, carbohydrate from lactose

• advantages
- easily digested, low renal solute load
- immunologic
  - reduction of acute illnesses (i.e. diarrhea, respiratory tract illnesses, acute otitis media) and may have longer term benefits
  - contains IgA, macrophages, active lymphocytes, lysozymes, lactoferrin (which inhibits E. coli growth in intestine)
  - lower pH promotes growth of Lactobacillus in GI tract
- parent-child bonding
- economical, convenient

• maternal contraindications
- absolute contraindications: HIV, HTLV type I and II, infant galactosemia
- relative contraindications: chemotherapy, radioactive compounds, or certain medications known to cross to breast milk with neonatal effects
- active untreated TB (2 wk), active HSV-2 lesions on breast (can still feed expressed breast milk from unaffected breast)

•if poor infant weight gain: consider dehydration or FTT and may consider formula supplementation if insufficient breastmilk production

•oral candidiasis (thrush): treat baby with antifungal such as nystatin and ensure all nipples, bottles, pacifiers are sanitized to avoid re-infection; can occur in breast or bottle-fed infants

Medications that Cross into Breast Milk
- Antimetabolites
- Chloramphenicol
- Diazepam
- Ergots
- Gold
- Metronidazole
- Tetracycline
- Lithium
- Cyclophosphamide

Signs of Inadequate Intake
- <6 wet diapers/d after first wk
- <7 feeds/d
- Sleepy or lethargic, sleeping throughout the night <6 wk
- Weight loss >10% of birth weight (past 10-14 d of life)
- Jaundice

Signs of Adequate Intake
- 1 wet diaper/d of age for first wk
- 1-2 black or dark green stools (meconium)/d on Day 1 and 2
- 3+ brown/green/yellow stools/d on Day 3 and 4
- 3+ yellow, seedy stools/d on Day 5+

Table 10. Common Formulas Compared to Breast Milk

Type of Nutrition	Indications	Content (as compared to breast milk)
Cow's Milk-Based (Enfamil®, Similac®)	Prematurity Transition to breastfeeding Contraindication to breastfeeding	Lower whey:casein ratio Plant fats instead of dietary butterfat
Fortified Formula	Low birth weight Prematurity	Higher calories and vitamins A, C, D, K May only be used in hospital due to risk of fat-soluble vitamin toxicity
Soy Protein (Isomil®, Prosobee®)	Galactosemia Desire for vegetarian/vegan diet*	Corn syrup solids or sucrose in place of lactose
Partially Hydrolyzed Proteins (Good Start®)	Delayed gastric emptying Risk of cow's milk protein allergy	Protein is 100% whey with no casein
Protein Hydrolysate (Nutramigen®, Alimentum®, Pregestimil®, Portagen®)	Malabsorption Food allergy including cow's milk protein allergy	Protein is 100% casein with no whey Corn syrup solids, sucrose, or tapioca starch instead of lactose Expensive
Amino Acid (Neocate®, PurAmino™)	Food allergy Short gut	Free amino acids (no protein) Corn syrup solids instead of lactose Very expensive
Metabolic	Inborn errors of metabolism	Various different compositions for children with galactosemia, propionic acidemia, etc.

* 10-35% of children with cow's milk protein allergy also have reactions to soy-based formula

Injury Prevention Counselling

- injuries are the leading cause of death in children >1 yr
- main causes: motor vehicle crashes, burns, drowning, falls, choking, infanticide

Table 11. Injury Prevention Counselling

0-6 mo	6-12 mo	1-2 yr	2-5 yr
Do not leave alone on bed, on changing table, or in tub Keep crib rails up Check water temperature before bathing Do not hold hot liquid and infant at the same time Check milk temperature before feeding Appropriate car seats are required before leaving hospital Avoid co-sleeping with infant Always position to sleep on back with no soft pillows or stuffed animals in crib	Install stair barriers Discourage use of walkers Avoid play areas with sharp-edged tables and corners Cover electrical outlets Unplug appliances when not in use Keep small objects, plastic bags, cleaning products, and medications out of reach Supervise during feeding Appropriate car seats Secure large items like televisions, dressers so they do not fall	Never leave unattended Keep pot handles turned to back of stove Caution with whole grapes, nuts, raw carrots, hotdogs, etc. due to choking hazard No running while eating Appropriate car seats Ensure never unattended in bath or in pool	Bicycle helmet Never leave unsupervised at home, driveway, or pool Teach bike safety, stranger safety, and street safety Swimming lessons (>4 yr), sunscreen (from 6 mo), fences around pools Appropriate car seats Ensure large devices (such as TVs) secured to walls

Note: This list is not exhaustive. For more details, see Rourke Baby Record (http://www.rourkebabyrecord.ca/downloads)

Circumcision

- elective procedure
  - CPS affirms that circumcision is not medically indicated, and does not recommend routine circumcision for every newborn male
  - often done for religious or cultural reasons
- **benefits**: prevention of phimosis and slightly reduced incidence of UTI, STI, balanitis, cancer of the penis
- **complications (<1%):** local infection, bleeding, urethral injury, meatal stenosis
  - complication rate increased in children compared with infants
- **contraindications**: presence of genital abnormalities (e.g. hypospadias) or known bleeding disorder

Newborn Male Circumcision
Pediatr Child Health 2015;20(6):311-320
There is some evidence that circumcision decreases urinary tract infections and incidence of some sexually transmitted infections, including HIV. While such a benefit may be present in high-risk populations, the Canadian Pediatric Society does not recommend routine circumcision as a medically indicated procedure for newborn males.

Common Complaints

Breath Holding Spells

- **clinical features**
  - cyanotic type (more common), usually associated with anger/frustration
  - pallid type, usually associated with pain/surprise
- **epidemiology:** 0.1-5% of healthy children 6 mo-4 yr, usually start during first yr of life
- **etiology**
  - cyanotic type: child is provoked (usually by anger or upsetting event) → holds breath and becomes silent → spontaneously resolves or loses consciousness
  - pallid type: child falls or is frightened → heart rate is reduced by vagal stimulation → cerebral hypoperfusion → loses consciousness
- **management**
  - usually resolves spontaneously and rarely progresses to seizure; median age of remission is 4 yr, and almost all children stop by 8 yr
  - help child control response to frustration and avoid drawing attention to spell
  - may be associated with iron deficiency anemia, improves with supplemental iron
  - if episodes prolonged/frequent, triggered by non-traumatic stimuli, or if there is a family history of syncope or sudden death → in-depth cardiac evaluation indicated - check for prolonged QT syndrome

Crying/Fussy Infant

- common etiologies: functional (e.g. hungry, irritable, lack of sleep), colic, trauma (e.g. accidental injury, non-accidental injury), illness, hair tourniquet
- history
  - description of baseline feeding, sleeping, crying patterns
  - infectious symptoms: fever, tachypnea, rhinorrhea, ill contacts
  - feeding intolerance: gastroesophageal reflux with esophagitis, N/V, diarrhea, constipation
  - physical injury (accidental or non-accidental), hair tourniquet on fingers/toes
  - recent immunizations (vaccine reaction) or medications (drug reactions), including maternal substances taken during pregnancy (i.e. neonatal withdrawal syndrome) or substances that may be transferred via breast milk

- inconsistent history, pattern of numerous emergency department visits, difficult social living conditions (e.g. parental substance use, precarious living circumstances) can raise concerns for maltreatment or non-accidental injury
- consider broad array of possible underlying causes such as meningitis, sepsis, respiratory distress, constipation, etc.

Infantile Colic

- **clinical features:** unexplained paroxysms of irritability and crying for >3 h/d, >3 d/wk for >3 wk in an otherwise healthy, well-fed baby (rule of 3s - Wessel criteria)
- **epidemiology:** 10% of infants; usual onset 10 d to 3 mo of age with peak at 6-8 wk
- **etiology:** unknown. Theories: alterations in fecal microflora, cow's milk intolerance, GI immaturity or inflammation, poor feeding, maternal smoking
- **diagnosis:** diagnosis of exclusion after thorough history and physical exam to rule out identifiable causes such as otitis media, cow's milk intolerance, GI problem, fracture, hair tourniquet
- **management**
  - parental relief, rest, support and reassurance are essential
  - change breastfeeding or bottle-feeding technique to minimize swallowing air
  - hold baby, soother, car ride, music, vacuum, check diaper
  - limited evidence for probiotics; further research required
  - breast-fed infants: time-limited trial (typically 1-2 wk) of a hypoallergenic maternal diet (i.e. no cow's milk, eggs, nuts, wheat) while monitoring baby's behaviour
  - formula-fed infants: time-limited trial (typically 1-2 wk) of hydrolyzed formula
  - prognosis: all resolve, most in the first 3-6 mo of life, no long-term adverse effects

Dentition and Caries

Dentition

- primary dentition (20 teeth)
  - first tooth at 5-9 mo (lower incisor), then 1/mo
  - 6-8 central teeth by 1 yr
  - assessment by dentist 6 mo after eruption of first tooth and certainly by 1 yr of age (Grade B recommendation)
- secondary dentition (32 teeth)
  - first adult tooth is 1st molar at 6 yr, then lower incisors

Caries

- early childhood caries: presence of one or more decayed, missing (due to caries), or filled tooth surfaces in any primary tooth in a preschool-aged child
- etiology: multifactorial with biomedical factors (e.g. diet, bacteria, host) and social determinants of health
  - inappropriate feeding practices (e.g. frequent, prolonged bottle feeding, putting to bed with bottle, prolonged breastfeeding, and excessive juice consumption) are important factors
- prevention
  - no bottle at bedtime, clean teeth after last feed
  - no juice or sweetened pacifier
  - clean gums with damp washcloth or soft-bristle toothbrush (no toothpaste) when no teeth present
  - <3 yr: daily brushing with fluoridated toothpaste (size of a grain of rice) as soon as teeth are present
  - 3-6 yr: assisted to brush teeth using pea sized amount of fluoridated toothpaste
  - ensure every child visits dentist by 1 yr
  - 1 yr and beyond: involve dental public health programs (e.g. Healthy Smiles in Ontario, Canada Dental Benefit) to support access for children in low-income households

Enuresis

Definition

- involuntary urinary incontinence by day and/or night in child >5 yr

General Approach

- should be evaluated if: dysuria; change in colour, odour, or stream; secondary or diurnal; change in gait; or stool incontinence are present

Primary Nocturnal Enuresis

- **clinical features:** enuresis when bladder control has never been attained
- **epidemiology:** 10% of children age 6, 3% of children age 12, 1% of children age 18, family history important
- **etiology:** developmental disorder or maturational lag in bladder control while asleep

Treatment for primary nocturnal enuresis should not be considered until 7 yr due to high rate of spontaneous cure

- **management**
  - time, reassurance (~20% resolve spontaneously each yr), and avoidance of punishment or humiliation to maintain self-esteem
  - behaviour modification (limiting fluids and avoid caffeine-containing food before bedtime, void prior to sleep, ensure access to toilet, take out of diapers)
  - conditioning: "wet" alarm wakes child upon voiding (70% success rate)
  - medications (for children >7 yr, considered second line, short-term therapy, may be used for sleepovers/camp): desmopressin (DDAVP) oral tablets (similar success rate as "wet" alarm therapy but higher relapse rate), imipramine (Tofranil®) (rarely used; lethal if overdose; side effects: cardiac toxicity, anticholinergic effects)

Secondary Enuresis

- **clinical features:** enuresis develops after child has sustained period of bladder control (>6 mo)
- **etiology:** inorganic regression due to stress or anxiety (e.g. birth of sibling, significant loss, family discord, sexual abuse), secondary to organic disease (UTI, DM, DI, sleep apnea, neurogenic bladder, CP, seizures, pinworms)
- **management:** treat underlying cause, specialist referral as appropriate

Diurnal Enuresis

- **clinical features:** daytime wetting (60-80% also wet at night)
- **etiology:** micturition deferral (holding urine until last minute) due to psychosocial stressor (e.g. shy), structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders, DM
- **management:** treat underlying cause, behavioural (scheduled toileting, double voiding, good bowel program, sitting backwards on toilet, charting/incentive system, relaxation/biofeedback), good constipation management, pharmacotherapy

Management and Treatment of Nocturnal Enuresis – An Updated Standardization Document from the International Children's Continence Society
J Pediatr Urol 2020;16(1):10-19
Additional investigations are not warranted in an enuretic child without certain warning signs. Key comorbidities to consider include psychiatric disorders, constipation, urinary tract infections, and snoring or sleep apneas. Treating constipation and daytime incontinence can lead to symptom resolution. Treating concomitant sleep disorder may also lead to symptom resolution and is indicated. If enuresis is non-monosymptomatic, treatment should begin with advice on evening drinking and voiding habits. In monosymptomatic enuresis, treatment should begin with either desmopressin or an enuresis alarm. Second line treatment includes anticholinergic medications. Antidepressants may be considered in refractory enuresis though expert opinion should be sought.

Encopresis

- **clinical features:** fecal incontinence in a child >4 yr, at least once per mo for 3 mo
- **prevalence:** 1-1.5% of school-aged children (rare in adolescence); M:F=6:1 in school-aged children
- **causes:** chronic constipation (retentive encopresis), Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, CP, hypotonia, anorectal malformations, bowel obstruction

Retentive Encopresis

- **definition:** child holds bowel movement, develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
- **etiology**
  - physical: painful stooling often secondary to constipation
  - emotional: parent-child stress, coercive toilet training, social stressors
- **clinical features**
  - history
    - crosses legs or stands on toes to resist urge to defecate
    - distressed by symptoms, soiling of clothes
    - toilet training coercive or lacking in motivation
    - may also hold urine
    - may show oppositional behaviour
    - abdominal pain
  - physical exam
    - digital rectal exam or abdominal x-ray: large fecal mass in rectal vault
    - anal fissures (result from passage of hard stools)
    - palpable stool in LLQ abdomen (50% of children with fecal incontinence)
    - staining of underwear with stool
- **management**
  - complete clean-out of bowel: PEG 3350 given orally is most effective and first line; enemas and suppositories may be second line therapies, but these are invasive, often less effective, and not recommended as first line
  - maintenance of regular bowel movements (see *Constipation, P46*)
  - assessment and guidance regarding psychosocial stressors
  - behavioural modification
- **complications:** recurrence, toxic megacolon (requires >3-12 mo to treat), bowel perforation

Toilet Training

- 90% of children attain bowel control before bladder control
- generally, females train earlier than males
- 25% by 2 yr (in North America), 98% by 3 yr have daytime bladder control
- signs of toilet readiness (usually 18-24 mo)
  - ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several hours (large enough bladder), can recognize need to go, able to remove clothing
- stepwise approach used to familiarize child with the potty chair and create a connection between elimination and the potty chair; praise with use of potty chair

Failure to Thrive

- **definition**
  - weight <3rd percentile, falls across two major percentile curves on growth chart, or <80% of expected weight for height and age
  - inadequate caloric intake most common factor in poor weight gain
  - may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
  - factors affecting physical growth: genetics, intrauterine factors, nutrition, endocrine hormones, chronic infections/diseases, psychosocial factors
- **clinical features**
  - history
    - nutritional intake
    - feeding behaviours
    - current symptoms
    - past illnesses
    - family history: growth, puberty, parental height and weight (including mid-parental height)
    - psychosocial history
  - physical exam
    - growth parameters, plotted
    - <2 yr: height, weight, head circumference
    - ≥2 yr: height, weight, BMI
    - vital signs
    - complete head to toe exam
    - dysmorphic features or evidence of chronic disease
    - upper to lower segment ratio
    - sexual maturity staging
    - signs of maltreatment or neglect
- **investigations** (as indicated by clinical features)
  - CBC, blood smear, electrolytes, T4, TSH, urea, ferritin, Ca^{2+}, celiac screen, and vitamins A, D, E, zinc
  - bone age x-ray
  - chromosomes/karyotype
  - chronic illness: chest (CXR, sweat Cl–), cardiac (CXR, ECG, echo), GI (celiac screen, inflammatory markers, malabsorption), renal (urinalysis), liver (enzymes, albumin)

Table 12. Failure to Thrive Patterns

Growth Parameters			Suggestive Abnormality
Decreased Wt	Normal Ht	Normal HC	Caloric insufficiency Decreased intake
Decreased Wt	Decreased Ht	Normal HC	Structural dystrophies Endocrine disorder
Decreased Wt	Decreased Ht	Decreased HC	Intrauterine insult

BA = bone age; CA = chronological age; HC = head circumference; Ht = height; Wt = weight

Etiology

- an interplay between pathophysiology and psychosocial influences
- investigations should assess:
  1. complex factors in the parent-child relationship
     - dietary intake, knowledge about feeding, improper mixing of formula
     - feeding environment
     - parent-child interaction, attachment
     - child behaviours (texture aversion, restrictive due to developmental diagnoses), hunger/satiety cues
     - postpartum depression
     - social factors: stress, poverty, neglect, child/domestic abuse, parental substance misuse, restricted diets
  2. inadequate caloric intake: inadequate milk supply/latching, mechanical feeding difficulty (cleft palate), oromotor dysfunction, toxin-induced anorexia
  3. inadequate absorption: biliary atresia, celiac, IBD, CF, inborn errors of metabolism, milk protein allergy, pancreatic cholestatic conditions

Mid-Parental Height

Boys target height = (father height + mother height + 13) /2

Girls target height = (father height + mother height – 13) /2
Note: height should be taken in cm

Clinical Signs of FTT

SMALL KID
Subcutaneous fat loss
Muscle atrophy
Alopecia
Lethargy
Lagging behind normal
Kwashiorkor
Infection (recurrent)
Dermatitis

Upper to Lower Segment Ratio

Increased in achondroplasia, short limb syndromes, hypothyroidism, storage diseases

Decreased in Marfan's, Klinefelter's, Kallman's syndromes, and testosterone deficiency

Calculation: upper segment/lower segment

Upper segment: top of head to pubic symphysis

Lower segment: pubic symphysis to floor

4. increased metabolism: chronic infection, CF, lung disease from prematurity, hyperthyroidism, asthma, IBD, malignancy, renal failure
5. increased losses
6. increased utilization (e.g. chromosomal disorders)
7. prenatal factors: placental insufficiency, intrauterine infections, genetic, maternal (e.g. pre-existing conditions like diabetes or renal disease; use of medications, drugs, tobacco, alcohol)

Management

- most as outpatient using multidisciplinary approach: primary care physician, occupational therapist, dietitian, psychologist, social work, CAS
- medical: oromotor problems, iron deficiency anemia, gastroesophageal reflux
- nutritional: educate about age-appropriate foods, calorie boosting, mealtime schedules, and environment; goal to reach 90-110% IBW, correct nutritional deficiencies, and promote catch-up growth/development
- behavioural: positive reinforcement, mealtime environment, no distractions (e.g. toys, books, or TV) during mealtime

Energy Requirements
- see *Nutrition, P8*

Obesity

- **definition**

Age	Overweight	Obese
0-2 yr	Weight for length >97th percentile	Weight for length >99.9th percentile
2-5 yr	BMI >97th percentile	BMI >99.9th percentile
5-19 yr	BMI >85th percentile	BMI >97th percentile

- risk factors: genetic predisposition (e.g. both parents obese – 80% chance of obese child), psychosocial/environmental contributors
- **etiology**
  - increased intake (dietary, social/behavioural, and iatrogenic such as drugs and hormones)
  - decreased energy expenditure
  - organic causes are rare (<5%): neuroendocrine (e.g. hypothyroidism, Cushing, PCOS), genetic (e.g. Prader-Willi, Carpenter, Turner Syndromes)
- **complications**: association with HTN, dyslipidemia, slipped capital femoral epiphysis, T2DM, asthma, OSA, gynecomastia, polycystic ovarian disease, early menarche, irregular menses, psychological trauma (e.g. bullying, decreased self-esteem, unhealthy coping mechanisms, depression)
- childhood obesity often persists into adulthood
- investigations: BP, pulse, screen for: dyslipidemia, fatty liver disease (ALT), T2DM (based on risk factors)
- **management**
  - encouragement and reassurance; engagement of entire family
  - diet: qualitative changes focused on optimizing nutrition (do not encourage weight loss, but allow for linear growth to catch up with weight), do not recommend special diets used by adults, alternative sweeteners, or very low calorie diets
  - behaviour modification: increase activity, change eating habits/meal patterns, portions, limit juice/sugary drinks, ensure adequate sleep
  - education: multidisciplinary approach, dietitian, counselling
  - surgery and pharmacotherapy are only considered after consultation with specialized providers
  - increase physical activity (1 h/d), reduce screen time (<2 h/d)
  - small changes in energy expenditure and intake (lose 1 lb/mo)
  - long term goal: maintain BMI <85th percentile

Poison Prevention

- keep all types of medicines, vitamins, and chemicals locked up in a secure container, out of sight, and out of reach
- potentially dangerous: medications, illicit drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- keep alcoholic beverages out of reach: 3 oz hard liquor can kill a 2 y/o
- always read labels before administering medicine to ensure correct medication drug and dose and/or speak with a pharmacist or healthcare provider

Perinatal and Early Childhood Factors for Overweight and Obesity in Young Canadian Children
C J Public Health 2013;104(1):e69-74
Purpose: To assess potential early-life factors and their interrelationships with obesity among young Canadian children.
Methods: Data from a nationally representative sample of children ages 6-11 in the Canadian Health Measures Survey were analyzed. The associations of perinatal and early childhood behaviours and socioeconomic factors with overweight or obesity were evaluated using multivariate logistic regression models.
Results: Of 968 term-born children, 21% were overweight and another 13% were obese. Maternal smoking during pregnancy was positively associated with obesity. This association was mediated by birth weight and once controlled, the strength of the association between smoking and child obesity increased by 12%. Birth weight per 100 g (1.05; 1.005-1.09) was significantly associated with obesity. Exclusive breastfeeding for 6 mo, adequate sleep hours, and being physically active were found to be protective. Breastfeeding, whether exclusive or not, significantly reduced obesity risk among children whose mothers never smoked in pregnancy.
Conclusion: This study identified multiple perinatal and childhood factors associated with obesity in young Canadian children. Effective prevention strategies targeting four modifiable maternal and child risk factors may reduce childhood obesity by up to 54% in Canada.

Screen Time Guidelines (Canadian Society for Exercise Physiology)
- Screen time is not recommended for children under 2 yr
- <1 h/d screen time is appropriate for children 2-5 yr
- <2 h/d screen time is appropriate for children 5-17 yr

Rashes

Table 13. Common Pediatric Rashes

Type of Rash	Differential	Appearance	Management
Diaper Dermatitis	Irritant contact dermatitis	Shiny, red macules/patches, no skin fold involvement	Eliminate direct skin contact with urine and feces, allow periods of rest without a diaper, frequent diaper changes, topical barriers (petrolatum, zinc oxide or paste), short-term low-potency topical corticosteroids (severe cases)
	Seborrheic dermatitis	Yellow, greasy macules/plaques on erythema, scales	Short-term, moisturisers, topical antifungal (ketoconazole), low-potency topical corticosteroids
	Candidal dermatitis	Erythematous macerated papules/plaques, satellite lesions, involvement of skin folds	Antifungal agents (e.g. clotrimazole, nystatin)
Other Dermatitis	Atopic dermatitis	Erythematous, papules/plaques, oozing, excoriation, lichenification, classic areas of involvement	Eliminate exacerbating factors, maintain skin hydration (daily baths and moisturisers), corticosteroids, topical calcineurin inhibitor (2nd line)
	Nummular dermatitis	Annular erythematous plaques, oozing, crusting	Avoid irritant if identified, potent topical steroid in emollient base, short-term systemic steroids ± antibiotics (severe)
	Allergic contact dermatitis	Red papules/plaques/vesicles/bullae, only in area of allergen	Mild: soothing lotion (e.g. calamine lotion) Moderate: low-to-intermediate potency topical corticosteroids Severe: systemic corticosteroids and antihistamine
	Irritant contact dermatitis	Morphology depends on irritant	Avoid skin contact
	Dyshidrotic dermatitis	Papulovesicular, cracking/fissuring, hands and feet ("tapioca pudding")	Mild/moderate: medium/potent topical corticosteroids Severe: systemic corticosteroids, local PUVA or UVA treatments
Infectious	Scabies	Polymorphic (red excoriated papules/nodules, burrows), in web spaces/folds, very pruritic Often affects multiple family members	Permethrin (Nix®) 5% cream for patient and family (2 applications, 1 wk apart)
	Impetigo	Honey-coloured crusts or superficial bullae	Mild: topical antibiotics (e.g. fucidic acid or mupirocin cream) Severe: oral antibiotics (e.g. cephalexin/erythromycin)
	Tinea corporis	Round erythematous plaques, central clearing and scaly border	Topical antifungal for skin, systemic antifungals for nails/head
Pediatric Exanthems (see *Infectious Pediatric Exanthems, P62*)			
Acne (see Dermatology, D14)			
Neonatal skin conditions (see *Skin Conditions of the Neonate, P82*)			

Sleep Disturbances

Types of Sleep Disturbances

- BEARS screening tool
- insufficient sleep quantity
  - difficulty falling asleep (e.g. limit setting sleep disorder)
    - preschool and older children
    - bedtime resistance
    - due to caregiver's inability to set consistent bedtime rules and routines
    - often exacerbated by child's oppositional behaviours
- poor sleep quality
  - frequent arousals (e.g. sleep-onset association disorder)
    - infants and toddlers
    - child learns to fall asleep only under certain conditions or associations (e.g. with parent, held, rocked or fed, with light on, in front of television), and loses ability to self-soothe
- OSA
  - **definition**: partial or intermittent complete airway obstruction during sleep causing disrupted ventilation and sleep pattern
  - **diagnostic criteria**: clinical suspicion (based on features like snoring, daytime sleepiness, and witnessed apneas, and/or risk factors like neuromuscular disorders and Down syndrome); a polysomnography is the gold standard for definite diagnosis

Daily Sleep Requirement	
<6 mo	16 h
6 mo	14.5 h
12 mo	13.5 h
2 yr	13 h
4 yr	11.5 h
6 yr	9.5 h
12 yr	8.5 h
18 yr	8 h
Nap Patterns	
2/d at 1 yr	
1/d at 2 yr (2-3 h long)	
0.5/d at 5 yr (1.7 h long)	

- **epidemiology**: 1-5% of preschool aged children, more common in Black children
- **clinical features**: snoring/gasping/noisy breathing during sleep and irritable/tired/hyperactive during the day
- **complications**: cardiovascular (HTN/LV remodelling due to sympathetic activation), growth, cognitive, and behavioural problems
- **etiology**: adenotonsillar hypertrophy, craniofacial abnormalities, obesity
- **investigations**: polysomnography can be done, but is not required (expensive, inaccessible); treatment can be initiated based on clinical judgement
- **management**: trial intranasal corticosteroids as temporizing measure in mild OSA; adenotonsillectomy and weight management are first-line tx, follow-up for residual OSA. Watchful waiting acceptable in mild-moderate cases
  - adenotonsillectomy does not improve executive function/attention, but improves behaviour, QOL, polysomnographic findings
  - use CPAP if adenotonsillectomy is contraindicated (cleft palate/bleeding disorder/acute tonsillitis), OSA with minimal adenotonsillar tissue, residual OSA
  - avoid pollutants/tobacco smoke, allergens
  - avoid use of corticosteroids and antibiotics

• parasomnias
- episodic nocturnal behaviours (e.g. sleepwalking, night terrors, nightmares)
- often involves cognitive disorientation and autonomic/skeletal muscle disturbance

Management of Sleep Disturbances
•set strict bedtimes and "wind-down" routines
•do not send child to bed hungry
•positive reinforcement for: limit setting sleep disorder
•always sleep in own bed, in a dark, quiet, and comfortable room
•avoid screens before bedtime and avoid caffeine-containing food
•do not use bedroom for timeouts
•systematic ignoring and gradual extinction for: sleep-onset association disorder

Nightmares
• **epidemiology**: common in boys, 4-7 yr
•associated with REM sleep (generally last one third of sleep)
• **clinical features**: upon awakening, child is alert and clearly recalls frightening dream ± associated with daytime stress/anxiety
• **management**: reassurance

Night Terrors
• **epidemiology**: 15% of children have occasional episodes
•usually in first one third of night; arousal from deep (slow wave) sleep
• **clinical features**: abrupt sitting up, eyes open, screaming/vocalization, occurs in early hours of sleep, stage 4 of sleep; signs of autonomic arousal with no memory of event, disoriented if awakened, inconsolable, stress/anxiety can aggravate them
• **management**: reassurance from parents, ensure child is safe (e.g. if sleepwalks), parents can try to identify pattern and wake up child 15 min before to disrupt pattern, often remits spontaneously before puberty

Sudden Infant Death Syndrome

Definition
• sudden and unexpected death of an infant <12 mo in which the cause of death cannot be found by history, examination, or a thorough postmortem and death scene investigation
• etiology: inherently unknown, but affected infants appear to have (1) underlying genetic or anatomic (e.g. brainstem abnormality) predisposition and (2) a trigger event (e.g. maternal smoking, airflow obstruction). SIDS tends to happen when (1) and (2) occur during a vulnerable stage of development

Epidemiology
• 0.5 in 1000 (leading cause of death between 1-12 mo); M:F=3:2
• more common in children placed in prone position
• in full term infants, peak incidence is 2-4 mo, 95% of cases occur by 6 mo
• increase in deaths during peak RSV season
• most deaths occur between midnight and 8 AM

Risk Factors
• maternal factors: young maternal age (<20 yr), smoking/alcohol/drug use during pregnancy, late/no prenatal care
• infant factors: prematurity (<37 wk), low birthweight, prone sleeping position, soft bedding (i.e. sleeping on soft surface and/or with blankets/pillows), sibling of a SIDS victim (5-6x increased risk of SIDS)
• environmental factors: exposure to second hand smoke, bed sharing, overheating, swaddling

Brief Resolved Unexplained Events (BRUE)
These are sudden, brief (<1 min) and now resolved episodes in an infant with one or more of the following: cyanosis or pallor; absent, decreased or irregular breathing; change in tone; and/or altered level of consciousness. The observer fears the child may be dying. The child should be asymptomatic on presentation. Evaluating for a cause of the BRUE (e.g. infection, cardiac, neurologic, child abuse, metabolic disease, toxins, etc.) is guided by history, physical exam, direct observation, and targeted investigations. An underlying etiology may be found in >50% of infants with BRUE.

Prevention
- "Back to Sleep, Front to Play" (place infant on back when sleeping, daily supervised play/"tummy time" in prone position)
- avoid sharing bed with infant
- avoid tobacco smoke exposure
- avoid overheating (e.g. use a fan) and overdressing
- appropriate infant bedding (firm mattress, avoid loose bedding, pillows, stuffed animals, and crib bumper pads)
- exclusive breastfeeding in first mo and no smoking
- pacifiers appear to have a protective effect; do not reinsert if falls out during sleep
- infant monitors do not reduce incidence
- immunizations appear to have a protective effect

Adolescent Medicine

Adolescent History (HEEADSSS)
- review confidentiality and its limits with adolescent prior to taking history
- tailor your history according to the clinical context
- Note that SSHADESS, a strength-based approach, may also be used as an approach to the adolescent history: *https://www.aap.org/contentassets/0e45de0366d54ec38fbfcb72382a0c6c/rt2e_ch32_sahm.pdf*

Home: Who do you live with? What kind of place do you live in? Do you get along with your parents and/or siblings? Is your home a safe place for you?

Education/Employment: What grade are you in? What are your favourite subjects? Tell me about your grades. How often do you miss school/class? Do you work (if so, how much)? Do you get along with teachers/employers?

Eating: Tell me about your meals/snacks in a typical day. Have you ever gone on a diet? What are your favourite and least favourite foods? (see Psychiatry, *Eating Disorders, PS39*)

Activities: What do you do after school? On the weekends? How much time do you spend on the computer/watching TV every day? Do you use social media (i.e. Facebook, Twitter, Instagram, etc.)? What do you do with your friends outside of school?

Drugs: Which seems to be more popular at your school, alcohol or drugs? How often do you drink/smoke cannabis or cigarettes/take other drugs? Have you ever passed out or not been able to remember what happened? Has anything bad ever happened to you while you were drunk or stoned?
- can organize as a CRAFFT screen: Ask Part A, questions 1-3. If yes to any, then ask 6 CRAFFT Part B questions. If no, then move on to Part B, question 1
  - Part A: during the last 12 mo, did you:
    1. Drink any alcohol?
    2. Smoke any cannabis, vape, or inhale any other substance?
    3. Use anything else to get high?
  - Part B:
    1. Have you ever ridden in a car driven by someone (including yourself) who was high or had been using drugs/alcohol?
    2. Do you ever use drugs/alcohol to relax, feel better about yourself, or fit in?
    3. Do you ever use drugs/alcohol when you are alone?
    4. Do you ever forget things you did while using drugs/alcohol?
    5. Do your family/friends ever tell you that you should cut down on your drinking or drug use?
    6. Have you ever gotten into trouble while you were using drugs/alcohol?
- can also use the SSHADESS framework for a trauma-informed approach to asking sensitive questions
- start with impersonal questions (e.g. "Are many of the teens in your school doing drugs?"), before asking personal questions (e.g. "Are you using any drugs?")
- see Psychiatry, *Substance-Related and Addictive Disorders, PS26*

Sexuality: What are your preferred pronouns? Do you have a crush on anyone? Do you have a partner? What does 'sex' mean to you? Have you ever had sex? Whether the answer is yes or no, the next question is: What activities would you include in the term 'having sex'? What do you do to prevent getting a STI/getting pregnant/getting someone pregnant? Has anyone ever given you money, drugs, or other stuff in exchange for sex? (see Gynecology, *Sexually Transmitted Infections, GY28*)

Suicidality/Depression: How would you describe your mood most days? On a scale of 1 to 10, where 1 is so sad that you might kill yourself and 10 is the happiest you could be, where are you most days? Have you lost interest in activities that you used to enjoy? Do you often have trouble sleeping (is there a difference between school days and the weekend?)? Have you ever thought seriously about suicide? Did you make a plan? (see Psychiatry, *Depression/Suicide, PS5*)

Safety/Violence: Do you ever get into a car with a driver who has been drinking or taking drugs? Do you always wear a seatbelt/bicycle helmet? Are you being bullied at school? Has anyone ever touched you in an unwanted way?

- ssee *Disorders of Sexual Development, P36*

Adolescent Psychosocial Assessment

HEEADSSS
Home
Education/Employment
Eating
Activities
Drugs
Sexuality
Suicide and depression
Safety/violence

Past yr drug use (%) in Ontario adolescents (2019): alcohol (41.7%), cannabis (22.0%), tobacco cigarettes (5.0%), electronic cigarettes (22.7%)

CRAFFT Screen
The CRAFFT is a well-validated substance use screening tool for adolescents 12-21 yr. See the CRAFFT website: crafft.org

Consent and Close Age Exceptions
- The legal age of consent to sexual activity is 16
- A youth 16 or 17 y/o cannot consent if: the partner is in a position of trust/authority (e.g. coach, teacher), young person is dependent on the partner (e.g. for care or support), the relationship is exploitative (e.g. prostitution or pornography)
- A 14 or 15 y/o can consent as long as the partner is less than 5 yr older and as long as there is no relationship of trust, authority, dependency, or exploitation
- A 12 or 13 y/o can consent as long as the partner is less than 2 yr older and as long as there is no relationship of trust, authority, dependency, or exploitation

Half of police-reported sexual offences are against children and youth

4.9% of Canadian youth (ages 12-17) have a mood disorder

Table 14. Developmental Stages of Adolescence

	Early Adolescence (10-13 yr)	Middle Adolescence (14-16 yr)	Late Adolescence (17-19 yr)
Cognitive and Moral	Concrete Unable to perceive long-term outcome of current decision-making	Emergence of abstract thought Questioning more	Future oriented with sense of perspective Idealism Ability to think things through independently
Self-Concept/Identity Formation	Preoccupied with changing body Self-consciousness about appearance and attractiveness	Concern with attractiveness "Stereotypical adolescent"	More stable body image Attractiveness may still be of concern Firmer identity
Family	Increased need for privacy	Conflicts over control and independence Struggle for acceptance of greater autonomy	Emotional and physical separation from family Increased autonomy
Peers	Seeks same-sex peer affiliation to counter instability	Intense peer group involvement Preoccupation with peers	Peer group and values recede in importance Intimacy/possible commitment takes precedence
Sexual	Increased interest in sexual anatomy Anxieties and questions about genital changes, size Limited dating and intimacy	Testing ability to attract partner Initiation of relationships and sexual activity Questions of sexual orientation	Consolidation of sexual identity Focus on intimacy and formation of stable relationships

Child Abuse and Neglect

Definition
- an act of commission (physical, sexual, or psychological abuse) or omission (neglect) by a caregiver that results in harm to a child or potential for harm

Legal Duty to Report
- upon reasonable grounds to suspect abuse and/or neglect, physicians are required by legislation to contact local child protection agencies to personally disclose all information relevant to the child's safety concern
- duty to report overrides patient confidentiality; physician is protected against liability

Ongoing Duty to Report
- if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the child protection agency must be made

Risk Factors
- important to remember that non-accidental injury and neglect can occur across all socio-economic strata
- environmental factors: social isolation, poverty, domestic violence
- caregiver factors: personal history of abuse, psychiatric illness, postpartum depression, substance misuse, single parent family, poor social and vocational skills, below average intelligence
- child factors: difficult temperament, disability, special needs (e.g. developmental delay), premature

Management of Physical Abuse, Child Abuse, and Neglect
- do not take an abuse history from a young child; this must be done by trained personnel (e.g. during a forensic interview)
- report all suspicions to the CAS; request emergency visit if imminent risk to child or any siblings in the home
- acute medical care: hospitalize for medical evaluation or treatment of injuries if indicated
- arrange consultation from social work and appropriate follow-up

Physical Abuse (Non-Accidental Injury)

History
- history that is not compatible with physical findings or with child's developmental capabilities
- history not reproducible or changes dramatically over time
- delay in seeking medical attention that is unexplained by other factors
- assess previous trauma or hospitalizations
- ask FHx: bleeding disorder, bone disorder, metabolic conditions
- ask developmental history

Physical Exam
- physical findings not explained by underlying medical condition
- assess growth parameters and compare to past recorded parameters (weight, height, head circumference)
- multiple injuries not explained by accidental injury or child's development level
- patterned skin injuries: linear, shapes, etc. that do not match provided history

- injury location:
  - bruises: on areas with abundant soft-tissue cushioning, such as the abdomen, buttocks, genitalia, fleshy part of cheek or on ears, neck, or feet,; bruises that do not fit described cause
  - fractures: posterior rib/metaphyseal/scapular/vertebral/sternal fractures
  - immersion burns (e.g. hot water)
- altered mental status: head injury, poisoning
- eyes: retinal hemorrhages
- scalp: patchy hair loss from traumatic alopecia or severe malnutrition
- oral exam: check the frenula for tears
- head trauma is the leading cause of death in child maltreatment (e.g. acceleration-deceleration forces (shaking), direct force application (blow or impact))
- consider "red herrings" (e.g. slate grey macule/congenital dermal melanocytosis vs. bruises; cupping practices that may look like bruising)

Investigations

- document all injuries on a body diagram: type, location, size, shape, colour, pattern
  - photography of skin injuries is ideal (police or hospital photography preferred; do not use physician's personal camera)
- rule out medical causes of bruising/fracture with appropriate investigations (e.g. blood disorders or rickets):
  - if fractures evident: Ca^{2+}, Mg^{2+}, PO_4^{3-}, ALP, PTH, Vitamin D, albumin
  - if bruising present: CBC, INR, PTT, von Willebrand factor, factors VIII/IX
- screen for abdominal trauma
  - elevated transaminases and amylase: abdominal CT recommended
  - renal function: electrolytes, urinalysis
    - toxicology screen: overdose or poisoning
- skeletal survey in children <2 yr; select imaging based on history in children >5 yr
  - neuroimaging: CT and/or MRI - dilated eye examination by pediatric ophthalmologist to rule out retinal hemorrhage if subdural hemorrhage detected on head imaging

Sexual Abuse

Definition

- any action where an older individual uses a child for sexual purposes, including sexual exploitation (e.g. trafficking)

Epidemiology

- peak at 2-6 yr and 12-16 yr; most do not report until adulthood
- as adults: more likely to develop obesity, sexual problems, IBS, fibromyalgia, STIs, substance use disorder
- more likely to experience intimate partner violence and sexual assault
  - in decreasing order of likelihood: family member, non-relative known to victim, stranger

History

- psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of trust, low self-esteem, school failure, sexually aggressive behaviour, advanced sexual knowledge, sexual preoccupation or play

Physical Exam

- recurrent UTIs, pregnancy, STIs, vaginitis, vaginal bleeding, pain, genital injury, enuresis
  - anogenital exam performed along with head-to-toe physical for physical trauma
  - instrumentation not required for anogenital exam; speculum contraindicated in prepubertal girls
  - most victims have normal anogenital exam – cannot rule out sexual abuse if exam is negative

Investigations

- depend on presentation, age, sex, and pubertal development of child
  - sexual assault examination kit within 24 h if prepubertal, within 72 h if pubertal
  - rule out STI, UTI, pregnancy (consider STI prophylaxis or emergency contraception)
  - rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)
  - drug and alcohol screen (e.g. Rohypnol, 'Liquid G,' etc.)

Medical Assessment of Bruising in Suspected Child Maltreatment Cases
Pediatr Child Health 2013;18(8):433-437
CPS Position Statement: While bruises are most often due to minor accidental injury, they may also signal underlying medical illness or inflicted injury. Knowing when to assess bruises in the context of maltreatment can be challenging. The following are red flags for inflicted injury in such bruising cases:

- Babies not yet cruising
- Present on ears, neck, feet, buttocks, or torso
- Not on the front of the body and/or overlying bone
- Unusually large or numerous
- Clustered or patterned
- Not fitting with the described causal mechanism

Neglect

Definition

- omissions in care by parents or caregiver that leads to actual or potential harm

History

- from child and each caregiver separately (if possible)

Physical Exam

- head to toe (do not force), growth parameters, nutrition status
- dental care
- emotional state

Investigations

- blood tests to rule out medical conditions or nutritional deficiencies (e.g. thrombocytopenia or coagulopathy)

Presentation of Neglect

FTT, developmental delay

Inadequate or dirty clothing, poor hygiene

Child exhibits poor attachment to parents, no stranger anxiety

Cardiology

Congenital Heart Disease

PRENATAL CIRCULATION

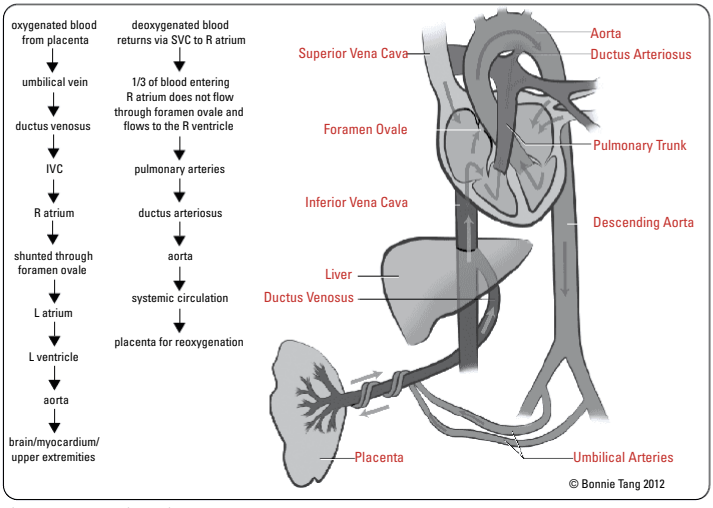

Figure 1. Prenatal circulation

Fetal circulation is designed so that oxygenated blood is preferentially delivered to the brain and myocardium

Before Birth

- shunting deoxygenated blood
  - ductus arteriosus: connection between pulmonary artery and aorta
- shunting oxygenated blood
  - foramen ovale: connection between right and left atria
  - ductus venosus: connection between umbilical vein and inferior vena cava

At Birth

- with first breath, lungs open up → pulmonary resistance decreases → pulmonic blood flow increases
- separation of low resistance placenta → systemic circulation becomes a high resistance system → ductus venosus closure
- increased pulmonic flow → increased left atrial pressures → foramen ovale closure
- increased oxygen concentration in blood after first breath → decreased prostaglandins → ductus arteriosus closure
- closure of fetal shunts and changes in vascular resistance → infant circulation assumes normal adult flow

Epidemiology

- 8 in 1000 live births have CHD, which may present as a heart murmur, heart failure, or cyanosis; VSD is the most common lesion

Investigations

- echo, ECG, CXR
- pre- and postductal oxygen saturations, 4 limb BPs, hyperoxia test

CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE

- cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 30 g/dL
- acyanotic heart disease (i.e. L to R shunt, obstruction occurring beyond lungs): blood passes through pulmonic circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis
- cyanotic heart disease (i.e. R to L shunt): blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis

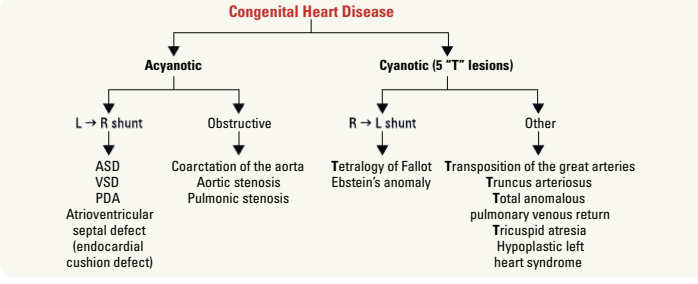

Figure 2. Common congenital heart diseases

Characteristic CXR Findings in CHD

Boot-shaped heart: tetralogy of Fallot, tricuspid atresia

Egg-shaped heart: transposition of great arteries

"Snowman" heart: total anomalous pulmonary venous return

Acyanotic Congenital Heart Disease

1. LEFT-TO-RIGHT SHUNT LESIONS

- extra blood is displaced through a communication from the left to the right side of the heart → increased pulmonary blood flow → increased pulmonary pressures
- shunt volume is dependent upon three factors: (1) size of defect, (2) pressure gradient between chambers or vessels, and (3) peripheral outflow resistance
- untreated shunts can result in pulmonary vascular disease, left ventricular dilatation and dysfunction, right ventricular HTN and RVH, and ultimately R to L shunts

Atrial Septal Defect

- **definition**: defect in the formation of the interatrial septum
- 3 types: ostium primum (common in DS, defect located at mitral or tricuspid valves), ostium secundum (most common type, 50-70%, defect located at septum between left and right atria), sinus venosus (defect located at entry of superior vena cava into right atrium)
- **epidemiology**: 6-8% of congenital heart lesions, common in patients with certain congenital disorders (e.g. DS, FAS)
- natural history
  - 80-100% spontaneous closure rate if ASD diameter <8 mm
  - if remains patent, CHF and pulmonary HTN can develop in adult life
- **clinical features**
  - history: often asymptomatic in childhood
  - physical exam: grade 2-3/6 pulmonic outflow murmur, widely split, and fixed S2
  - children with large ASDs may have signs of heart failure (tachypnea, FTT, hepatomegaly, pulmonary rales/retractions)
- **investigations**
  - ECG: RAD, mild RVH, RBBB (normal ECG does not rule out)
  - CXR: increased pulmonary vasculature, cardiac enlargement (normal ECG does not rule out)
  - echo: diagnostic
- **management**
  - elective surgical or catheter closure between 2-5 yr, though majority require no surgery
  - size <8 mm will likely spontaneously close

Ventricular Septal Defect

- definition: defect in the formation of the ventricular septum
- most common congenital heart defect (30-50%)
- small VSD (majority)
  - **clinical features**
    - history: asymptomatic, normal growth, and development
    - physical exam: early systolic to holosystolic murmur, best heard at LLSB, thrill
  - **investigations**: echo to confirm diagnosis (ECG and CXR are normal)
  - **management**: most close spontaneously
- moderate-to-large VSD
  - **epidemiology**: CHF by 2 mo; late secondary pulmonary HTN if left untreated

Moderate-to-Large VSD

Size of VSD is inversely related to sound of murmur (loud murmur = smaller hole)

- **clinical features**
  - history: delayed growth, decreased exercise tolerance, recurrent URTIs or "asthma" episodes
  - physical exam: holosystolic murmur at LLSB, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur, loss of splitting of second heart sound and a loud P2 suggests pulmonary hypertension
- **investigations**
  - ECG: LVH, LAH, RVH (normal ECG does not rule out)
  - CXR: increased pulmonary vasculature, cardiomegaly, CHF (normal CXR does not rule out)
  - echo: diagnostic
- **management**: treatment of CHF and surgical closure by 1 yr, if surgery required

Patent Ductus Arteriosus

- patent vessel between descending aorta and left pulmonary artery (normally, functional closure within first 15 h of life, anatomical closure within first days of life)
- **epidemiology**
  - 5-10% of all congenital heart defects
  - delayed closure of ductus is common in premature infants (1/3 of infants <1750 g); this is different from PDA in term infants
- **natural history**: PDA is usually associated with immaturity in premature infants, but is typically associated with a functional defect in term infants. As such, spontaneous closure is less common in term infants
- **clinical features**
  - history: asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use, CHF
  - physical exam: tachycardia ± gallop rhythm, bounding pulses, hyperactive precordium, wide pulse pressure, continuous "machinery" murmur best heard at left infraclavicular area
- **investigations**
  - ECG: may show left atrial enlargement, LVH, RVH
  - echo is diagnostic
  - CXR: may show normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery
- **management**
  - indomethacin (Indocid*): antagonizes prostaglandin E2, which maintains ductus arteriosus patency; only effective in premature infants
  - catheter or surgical closure if PDA causes respiratory compromise, FTT, or persists beyond 3rd mo of life

Figure 3. Patent ductus arteriosus

2. OBSTRUCTIVE LESIONS

- present with decreased urine output, pallor, cool extremities and poor pulses, shock, or sudden collapse

Coarctation of the Aorta

- **definition**: narrowing of aorta (almost always at the level of the ductus arteriosus)
- **epidemiology**: commonly associated with bicuspid aortic valve (50%); Turner syndrome (35%)
- **clinical features**
  - history: often asymptomatic
  - physical exam
    - blood pressure discrepancy between upper and lower extremities (increased suspicion/ severity if >20 mmHg difference)
    - diminished or delayed femoral pulses relative to brachial pulses (i.e. brachial-femoral delay)
    - possible systolic murmur with late peak at apex, left axilla, and left back
    - if severe, presents with shock in the neonatal period when the ductus arteriosus closes
- **investigations**: ECG shows RVH early in infancy, LVH later in childhood; echo or MRI for diagnosis
- **prognosis**: can be complicated by HTN; if associated with other lesions (e.g. PDA, VSD) can lead to CHF
- **management**: give prostaglandins to keep ductus arteriosus patent for stabilization and perform surgical correction in neonates; for older infants and children balloon arterioplasty may be an alternative to surgical correction

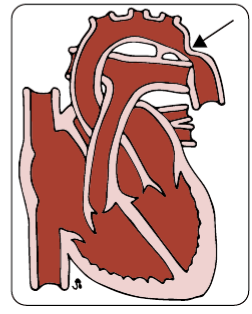

Figure 4. Coarctation of the aorta

Aortic Stenosis

- **definition**: defect that causes narrowing/stiffening of the aortic valve obstructing the blood flow between the left ventricle and the aorta
- 4 types: valvular (75%), subvalvular (20%), supravalvular, and idiopathic hypertrophic subaortic stenosis (5%)
- **clinical features**
  - history: often asymptomatic, but may be associated with CHF, exertional chest pain, syncope, or sudden death
  - physical exam: SEM at RUSB with aortic ejection click at the apex (only for valvular stenosis)
- **investigations**: echo for diagnosis
- **management**: valvular stenosis is usually treated with balloon valvuloplasty, patients with subvalvular or supravalvular stenosis require surgical repair, exercise restriction required

Pulmonary Stenosis

- **definition**: defect that causes narrowing/stiffening of the pulmonic valve obstructing the blood flow between the right ventricle and the pulmonary artery
- 3 types: valvular (90%), subvalvular, or supravalvular
- **definition of critical pulmonary stenosis**: inadequate pulmonary blood flow, dependent on ductus arteriosus for oxygenation, progressive hypoxia and cyanosis
- **natural history**: may be part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with syndromes (e.g. congenital rubella, Noonan syndrome)
- **clinical features**
  - history: spectrum from asymptomatic to CHF
  - physical exam: wide split S2 on expiration, SEM at LUSB, pulmonary ejection click (for valvular lesions)
- **investigations**
  - ECG findings: RVH
  - CXR: post-stenotic dilation of the main pulmonary artery (due to high velocity jet past stenotic valve)
  - echo: diagnostic
- **management**: surgical repair if critically ill or if symptomatic in older infants/children

Cyanotic Congenital Heart Disease

- systemic venous return re-enters systemic circulation directly
- most prominent feature is cyanosis (O_2 saturation <75%)
- hyperoxic test differentiates between cardiac and other causes of cyanosis
  - obtain preductal, right radial ABG in room air, then repeat after the child inspires 100% O_2
  - if PaO_2 improves to >150 mmHg, cyanosis less likely cardiac in origin
- pre-ductal and post-ductal pulse oximetry
  - >5% difference suggests R to L shunt

Causes of Cyanotic Heart Disease – 5Ts
Truncus arteriosus
Transposition of the great vessels
Tricuspid atresia
Tetralogy of Fallot
Total anomalous pulmonary venous return

Tetralogy of Fallot
1. VSD
2. RVOTO
3. Aortic root "overriding" VSD
4.RVH

1. RIGHT-TO-LEFT SHUNT LESIONS

Tetralogy of Fallot

- **epidemiology**: 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy with peak incidence at 2-4 mo
- **pathophysiology**
  - embryological defect due to anterior and superior deviation of the outlet septum leading to: VSD, RVOTO (i.e. pulmonary stenosis ± subpulmonary valve stenosis), overriding aorta, and RVH
    - infants may initially have a L → R shunt (therefore no cyanosis); however, RVOTO is progressive, leading to increasing R → L shunting with hypoxemia and cyanosis
    - degree of RVOTO determines the direction and degree of shunt and, therefore, the extent of clinical cyanosis and degree of RVH
- **clinical features**
  - history: hypoxic "tet" spells
    - during exertional states (crying, exercise) the increasing pulmonary vascular resistance and decrease in systemic resistance causes an increase in right-to-left shunting
    - clinical features include paroxysms of rapid and deep breathing, irritability and crying, increasing cyanosis, decreased intensity of murmur (decreased flow across RVOTO), patient squatting for relief (increased peripheral resistance, decreased R to L shunting)
    - if severe, can lead to decreased level of consciousness, seizures, death
  - physical exam
    - single loud S2 due to severe pulmonary stenosis (i.e. RVOTO), SEM at LLSB
- **investigations**
  - ECG: RAD, RVH
  - CXR: boot-shaped heart, decreased pulmonary vasculature, right aortic arch (in 25%)
  - echo: diagnostic
- **management of spells**: O_2, knee-chest position, fluid bolus, morphine sulfate, propranolol, phenylephrine
- **treatment**: surgical repair at 4-6 mo of age; earlier if marked cyanosis or "tet" spells

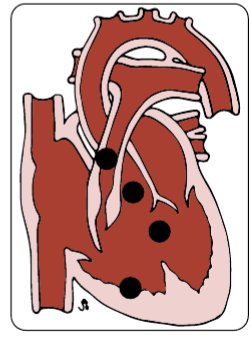

Figure 5. Tetralogy of Fallot

2. OTHER CYANOTIC CONGENITAL HEART DISEASES

Transposition of the Great Arteries

- **epidemiology**: 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonates
- **pathophysiology**: parallel pulmonary and systemic circulations
  - systemic: body → RA → RV → aorta → body
  - pulmonary: lungs → LA → LV → pulmonary artery → lungs
  - survival is dependent on mixing through PDA, ASD, or VSD
- **physical exam**
  - neonates: ductus arteriosus closure causes rapidly progressive severe hypoxemia unresponsive to oxygen therapy, acidosis, and death
  - VSD present: cyanosis is not prominent; CHF within first weeks of life
  - VSD absent: no murmur

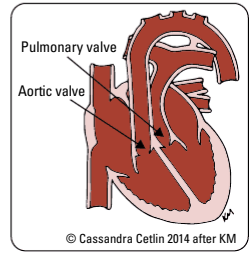

Figure 6. Transposition of the great arteries

- **investigations**
  - ECG: RAD, RVH, or may be normal
  - CXR: egg-shaped heart with narrow mediastinum ("egg on a string")
  - echo: diagnostic
- **management**
  - symptomatic neonates: prostaglandin E1 infusion to keep ductus open until balloon atrial septostomy
  - surgical repair: arterial switch performed in the first 2 wk in those without a VSD while LV muscle is still strong

Total Anomalous Pulmonary Venous Return

- **epidemiology**: 1-2% of CHD
- **pathophysiology**
  - all pulmonary veins drain into right-sided circulation (systemic veins, RA)
  - no direct oxygenated pulmonary venous return to left atrium
  - often associated with obstruction at connection sites
  - ASD must be present for oxygenated blood to shunt into the LA and systemic circulation
- **management**: surgical repair in all cases and required urgently for severe cyanosis

Truncus Arteriosus

- **pathophysiology**
  - single great vessel gives rise to the aorta, pulmonary, and coronary arteries
  - truncal valve overlies a large VSD
  - potential for coronary ischemia with fall in pulmonary vascular resistance
- management: surgical repair within first 6 wk of life

Hypoplastic Left Heart Syndrome

- **epidemiology**: 1-3% of CHD; most common cause of death from CHD in first mo of life
- **pathophysiology**: LV hypoplasia may include atretic or stenotic mitral and/or aortic valve, small ascending aorta, and coarctation of the aorta with resultant systemic hypoperfusion
- systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
- **management**
  - intubate and correct metabolic acidosis
  - IV infusion of prostaglandin E1 to keep ductus open
  - surgical palliation (overall survival 50% to late childhood) or heart transplant

Ebstein's Anomaly

Septal and posterior leaflets of tricuspid valve are malformed and displaced into the RV

Potential for RV dysfunction, tricuspid stenosis, tricuspid regurgitation, or functional pulmonary atresia if RV unable to open pulmonic valves

Accessory conduction pathways (e.g. WPW) are often present

Etiology

Unknown, heterogeneous genetic predisposition, associated with maternal lithium and benzodiazepine use in 1st trimester

Treatment

Newborns: consider closure of tricuspid valve + aortopulmonary shunt, or transplantation

Older children: tricuspid valve repair or valve replacement + ASD closure

4 Features of Hypoplastic Left Heart Syndrome

Hypoplastic LV

Narrow mitral/aortic valves

Small ascending aorta

Coarctation of the aorta

Congestive Heart Failure

- see Cardiology and Cardiac Surgery, C40

Etiology

- CHD
- cardiomyopathy (primary or secondary)
- high output circulatory states (e.g. anemia, AVMs, cor pulmonale, hyperthyroidism)
- non-cardiac (e.g. sepsis, renal failure)
- pressure overload (e.g. aortic stenosis/coarctation, pulmonary stenosis, HTN)
- volume overload (e.g. L to R shunt, valve insufficiency)

Clinical Features

- infant: weak cry, irritability, feeding difficulties, early fatigability, diaphoresis while sleeping or eating, respiratory distress, lethargy, FTT
- child: decreased exercise tolerance, fatigue, decreased appetite, respiratory distress, frequent URTIs, or "asthma" episodes
- orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all uncommon in children
- physical findings: 4 key features (tachycardia, tachypnea, cardiomegaly, hepatomegaly). Additionally, FTT, alterations in peripheral pulses, four limb blood pressures (in some CHDs), dysmorphic features associated with congenital syndromes, gallop rhythm

Investigations

- CXR: cardiomegaly, pulmonary venous congestion
- ECG: sinus tachycardia, signs of underlying cause (heart block, atrial enlargement, hypertrophy, ischemia/infarct)
- echo: structural and functional assessment
- blood work: CBC, electrolytes, BUN, Cr, LFTs

Management

- general: sitting up, O_2, sodium and water restriction, increased caloric intake
- pharmacologic: diuretics, afterload reduction (e.g. ACEI), β-blockers; digoxin rarely used
- curative: correction of underlying cause

4 Key Features of CHF

2 Tachys and 2 Megalys

Tachycardia

Tachypnea

Cardiomegaly

Hepatomegaly

Dysrhythmias

- can be transient or permanent, congenital (structurally normal or abnormal), or acquired (toxin, infection, infarction)

Sinus Arrhythmia
- phasic variations with respiration (present in almost all normal children)

Sinus Tachycardia
- rate of impulses arising from sinus node is elevated (>150 bpm in infants, >100 bpm in older children)
- characterized by: beat-to-beat heart rate variability with changes in activity, P waves present/normal, PR constant, QRS narrow
- etiology: HTN, fever, anxiety, sepsis, anemia/hypoxia, pain, PE, drugs, etc.
- differentiate from SVT by slowing the sinus rate (vagal massage, β-blockers) to identify sinus P waves

Premature Atrial Contractions
- may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitalis toxicity

Premature Ventricular Contractions
- common in adolescents
- benign if single, uniform, disappear with exercise, and no associated structural lesions
- if not benign, may degenerate into more severe dysrhythmias

Supraventricular Tachycardia
- abnormally rapid heart rhythm originating above the ventricles – most frequent sustained dysrhythmia in children
- no beat-to-beat HR variability, >220 bpm (infants) or >180 bpm (children), P waves absent/abnormal, PR indeterminable, QRS usually narrow
- pre-excitation syndromes (subset of SVT): WPW syndrome, congenital defect (see Cardiology and Cardiac Surgery, C9)

Complete Heart Block
- congenital heart block can be caused by maternal anti-Ro or anti-La (e.g. mother with SLE)
- often diagnosed in utero (may lead to development of fetal hydrops)
- clinical symptoms related to level of block (the lower the block, the slower the heart rate and greater the symptoms of inadequate cardiac output)
- symptomatic patients need a pacemaker

Pediatric vs. Adult ECG
Pediatric ECG findings that may be normal:
- HR >100 bpm
- Shorter PR and QT intervals and QRS duration
- Inferior and lateral small Q waves
- RV larger than LV in neonates, so normal to have:
  - RAD
  - Large precordial R waves
  - Upright T waves
  - Inverted T waves in the anterior precordial leads from early infancy to teen years

Heart Murmurs

- 50-80% of children have audible heart murmurs at some point in their childhood
- most childhood murmurs are functional (e.g. "innocent") without associated structural abnormalities and have normal ECG and radiologic findings
- in general, murmurs can become audible or accentuated in high output states (e.g. fever, anemia)

Table 15. Differentiating Heart Murmurs

	Innocent	Pathological
History and Physical	Asymptomatic	Symptoms and signs of cardiac disease (FTT, exercise intolerance)
Timing	SEM	All diastolic, pansystolic, or continuous (except venous hum)
Grade/Quality	<3/6; soft/blowing/vibratory	≥3/6 (palpable thrill); harsh
Splitting	Physiologic S2	May have fixed split or single S2
Extra Sounds/Clicks	None	May be present
Change of Position	Murmur varies	Unchanged

Table 16. Five Innocent Heart Murmurs

Type	Etiology	Location	Timing	Description	Age	Differential Diagnosis
Peripheral Pulmonic Stenosis	Flow into pulmonary branch arteries from main, larger, artery	Left upper sternal border	Systolic ejection	Neonates, low-pitched, radiates to axilla and back	Neonates, usually disappears by 3-6 mo	PDA Pulmonary stenosis
Still's Murmur	Flow across the pulmonic valve leaflets	Left lower sternal border	Systolic ejection	High-pitched, vibratory, LLSB or apex, SEM	3-6 yr	Subaortic stenosis Small VSD
Venous Hum	Altered flow in veins	Infraclavicular (R>L)	Continuous	Infraclavicular hum, continuous, R>L	3-6 yr	PDA
Pulmonary Flow	Flow through the pulmonic valve	Left upper sternal border	Systolic ejection	Soft, blowing, LUSB, SEM	8-14 yr	ASD Pulmonary stenosis
Supraclavicular Arterial Bruit	Turbulent flow in the carotid arteries	Supraclavicular	Systolic ejection	Low intensity, above clavicles	Any age	Aortic stenosis Bicuspid aortic valve

Infective Endocarditis

- see Infectious Diseases, ID15

Development

Global Developmental Delay

•also known as Early Developmental Impairment

Definition

•significant delay (at least 2 SDs below the mean with standardized tests) in at least 2 developmental domains (gross motor, fine motor, speech/language, cognitive, social/personal, activities of daily living) in a child <5 yr
•may predict a diagnosis of intellectual disability in the future
•after age 5, intellectual and physical disabilities are described (no longer a development 'delay' as catch up is not expected)

Epidemiology

•up to 3% of pediatric population; 40-80% of cases have a defined etiology

Table 17. Etiology of Global Developmental Delay

Broad Category	Possible Causes	Upper Limit of Diagnostic Yield*
Prenatal Biological Factors	Genetic abnormalities Central nervous system deformities Metabolic issues	47%
Prenatal Environmental Factors	Teratogens/toxins (substances of abuse, medications, etc.) Infections	21%
Perinatal	Asphyxia and neonatal encephalopathy Premature birth Low birth weight Neonatal complications	55%
Postnatal	Neglect/unhealthy psychosocial environment Infections Trauma Severe jaundice (kernicterus) Toxins	11%

*Percentage of total cases of GDD or ID with an identified etiologic diagnosis who fall into this specific category

Clinical Features
- key questions in addition to standard pediatric history:
  - detailed developmental history including milestones, rate of acquisition, regression of skills
  - detailed prenatal, birth, postnatal history
  - detailed three-generation family history
  - detailed psychosocial history, including exposure to environmental toxins
  - associated problems: feeding, seizures, behaviour, sleep
- physical exam
  - micro/macrocephaly, hepatosplenomegaly, height, and weight
  - **neurodevelopmental exam** (neurological exam, congenital abnormalities, dysmorphic features head-to-toe, cutaneous findings, dysmorphic features, current developmental level)
- investigations (guided by history, physical examination, and CPS stepwise algorithm)
  - refer for formal vision and hearing tests, which may guide further management
  - first line: chromosomal microarray and Fragile X DNA testing
  - "Tier 1" lab investigations (defined by CPS) for inborn errors of metabolism:
    - blood: CBC, glucose, blood gas, urea, creatinine, electrolytes with anion gap, AST, ALT, TSH, CK, ammonia, lactate, amino acids, acylcarnitine profile, carnitine, homocysteine, copper, ceruloplasmin, biotinidase
    - urine: organic acids, creatine metabolites, purines, pyrimidines, glycosaminoglycans
  - additional investigations: ferritin, B12, lead, congenital infections
  - brain imaging: microcephaly, macrocephaly, seizures, or abnormal neurological findings
  - consider consultation with genetics or endocrinology

Management
- dependent on specific area of delay
- therapy services (e.g. speech and language therapy for communication delay, OT and/or PT for motor delay), early intervention services (e.g. infant development services, drop-in programs; preschool); access to daycare supports development

Intellectual Disability

Definition
- characterized by three domains: deficits in intellectual function (confirmed by clinical assessment and standardized intelligence testing, historically defined as Intelligence Quotient (IQ) <70), deficits in adaptive function, and symptom onset during developmental period
- severity levels (mild, moderate, severe, profound) are based on adaptive function, not IQ

Epidemiology
- 1-3% of general population; M:F=1.5:1

Clinical Features
- history
  - earlier age of onset correlates with greater severity of ID
  - well below average general intellectual functioning
  - significant deficits in adaptive functioning in at least 2 of: communication, self-care, home-living, social skills, self-direction, academic skills, work, leisure, health, safety
- physical exam
  - check growth, dysmorphic features, complete physical exam, detailed observation of behaviour/phenotype (i.e. social skills)
- investigations
  - standardized psychoeducational assessment (includes cognitive and adaptive functioning measures); performed by psychologists
  - vision, hearing, and/or neurologic assessment
  - genetic and metabolic testing as indicated

Management
- main objective: enhance adaptive functioning level
- requires an interprofessional team with strong case coordination
- emphasize community-based treatment and early intervention
- behaviour management services, therapy services (e.g. OT, SLP), medications for associated conditions
- medications for associated conditions
- education: life skills, vocational training, communication skills, family education
- psychosocial support for individual and family; financial support; respite care, individual/family therapy

Prognosis
- higher rates of sensory deficits, motor impairment, behavioural/emotional disorders, seizures, psychiatric illness
- at increased risk of abuse/neglect

Language Delay

Definition
- no universally accepted definition, but most often identified around 18 mo of age with enhanced well baby visit
- if formally tested, at least one standard deviation below mean of age on standardized testing
- can be expressive (ability to produce or use language), receptive (ability to understand language), or both

Epidemiology
- M>F
- ~10-15% of 2 y/o children have a language delay, but only 4-5% remain delayed after age 3
- ~6-8% of school-aged children have specific language impairment (many of whom were not identified before school entry)

Etiology
- intellectual disability
- selective mutism
- language specific learning disorder
- isolated language delay
- developmental disorders: cerebral palsy, autism spectrum disorder, constitutional language delay
- genetic/metabolic: DS, Fragile X syndrome, Williams syndrome, hypothyroidism, PKU, etc.
- mechanical problems: cleft palate, cranial nerve palsy, hearing impairment
- medical conditions: seizure disorder (includes acquired epileptic aphasia), degenerative neurologic disorders (i.e. Rett syndrome, Leigh encephalopathy), CP, TORCH infection, iron deficiency, lead poisoning, etc.
- psychosocial: limited exposure to enriching environments; neglect or abuse

Clinical Features
- history
  - concerns about hearing, delay in language development or regression in previously normal language development
  - delayed language milestones, presence of red flags, regression (see *Table 9, Developmental Milestones, P8*)
  - must determine if language delay is expressive, receptive, or mixed
  - assess social communication skills, including use of gestures
  - determine differences in behaviour at home, school, other social environments
  - risk factors: family history of speech and language delay, male, prematurity, low birth weight, hearing loss
- physical exam
  - guided by history: look for abnormal growth, dysmorphisms, unusual social interactions (lack of eye contact, not pointing)
  - include full exam of the external/internal ear (e.g. TM scarring), oral pharynx (e.g. cleft palate), and neurologic system (including tone)
- investigations
  - use of language specific screens in primary care setting: The Early Language Milestone, Communication and Symbolic Behaviour Scales Developmental Profile Infant-Toddler Checklist, Ages and Stages Questionnaire (ASQ), Nippising District Developmental Screen (NDDS)
  - Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS), Modified Checklist for Autism in Toddlers (M-CHAT), etc.
  - developmental evaluation and observation during informal interaction
  - hearing, dental, and vision screening (audiology, dentistry, and optometry referral)
  - CBC, ferritin (to rule out anemia), venous blood lead levels, genetic/metabolic workup as indicated

Risk Factors for Sensorineural Hearing Loss

Genetic syndromes/family history

Congenital (TORCH) infections

Craniofacial abnormalities

<1500 g birth weight

Hyperbilirubinemia/kernicterus

Asphyxia/low APGAR scores

Bacterial meningitis, viral encephalitis

Management
- specific to etiology
- referral to SLP most important, consider referral to Otolaryngology (ENT), dental professionals, general support services like attending daycare or preschool
- consider other interventions specific to etiology
- prevention: parents can read aloud to their child daily, narrate daily activities, attend early education drop-in programs, preschool/daycare, etc.

Primary care physicians should also suspect a receptive language delay in any young child with an expressive language delay

Prognosis
- depends on etiology – best prognosis for developmental speech delay
- if language delay persists beyond age 5, more likely to have difficulties in adulthood
- persistent language delay is associated with poor academic performance, behavioural problems, social isolation

Specific Learning Disorder

Definition
- specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
- a significant discrepancy between a child's intellectual ability and their academic performance
- types: reading (dyslexia), writing, mathematics (dyscalculia)

Epidemiology
- prevalence: 10% (most commonly dyslexia)
- high incidence of psychiatric comorbidity: anxiety, dysthymia, conduct disorder, major depressive disorder, oppositional defiant disorder, ADHD

Etiology
- pathogenesis is unknown, likely genetic factors involved
- learning disabilities may be associated with a number of conditions:
  - genetic/metabolic (e.g. Turner syndrome, Klinefelter syndrome)
  - perinatal: prematurity, low birth weight, birth trauma/hypoxia
  - postnatal: CNS damage, hypoxia, environmental toxins, FAS, psychosocial deprivation (understimulation), malnutrition
- poor visual acuity is NOT a cause

Risk Factors
- positive family history, prematurity, developmental and mental health conditions, neurologic disorders (e.g. seizure disorders, neurofibromatosis), history of CNS infection/irradiation/traumatic injury, prenatal alcohol exposure, chromosomal disorders

Clinical Features
- history and physical exam
  - school difficulties (academic achievement, behaviour, attention, social interaction, over-reliance on teacher)
  - consider exposure to formal education particularly for newcomer children; can appear to have educational problems due to new environment; LD more suggestive if on history may have had education difficulties in previous countries of residence or does not improve after at least 18 months in new educational setting
  - development of negative self-concept → reluctance to participate even in areas of strength
  - social issues: overt hostility towards parents/teachers; difficulties making friends, bullying, and anxiety
  - look for dysmorphisms, complete physical exam; signs and symptoms of OSA
- investigations
  - psychoeducational assessment, educational history from school staff
  - individual scores on achievement tests in reading, mathematics, or written expression (WISC III, WRAT) >2 SD below that expected for age, education, and IQ
  - evaluate attention, memory, expressive language, coordination skills

Management
- provide quality instruction for specific learning disability
- advocate for school supports: modifying the curriculum and/or providing accommodations (e.g. scribe for writing, extra time for tests, photocopied notes, etc.)
- Individualized Education Plan (IEP): a written plan that describes the strength and needs of the student, services established to meet these needs, and how these services should be delivered
- specialized education placements that can provide educational remediation

Prognosis
- limited information available about persistence of learning disabilities over time
- low self-esteem, poor social skills, 40% school drop-out rate

Fetal Alcohol Spectrum Disorder

Definition
- term describing the range of effects of prenatal exposure to alcohol, including physical, mental, behavioural, and learning disabilities
- spectrum from most to least severe: FAS (fetal alcohol syndrome), partial FAS, ARBD (alcohol related birth defects), and ARND (alcohol related neurodevelopmental disorder)

Epidemiology
- prevalence of FAS and FASD is 0.1% and 1.0%, respectively
- most common preventable cause of intellectual disability
- CDC estimates 10% of women drink alcohol during pregnancy, although abstinence is strongly recommended

Pathogenesis
- specific mechanism of FASD is unknown, but hypotheses include nutritional deficits, toxic effects of acetaldehyde, alteration of placental transport, abnormal protein synthesis, and altered cerebral neurotransmission

Diagnosis
- often misdiagnosed or missed entirely
- multidisciplinary team needed to make diagnosis and involves a complex physical exam and neurodevelopmental assessment
- criteria for diagnosis of FAS – can be with or without sentinel facial features
  - FASD with sentinel facial features: 1. presence of facial features, 2. maternal alcohol consumption confirmed or unknown, 3. evidence of neurodevelopmental impairment OR microcephaly in infants and young children
  - FASD without sentinel facial features: evidence of neurodevelopmental impairment, maternal alcohol consumption confirmed
  - sentinel facial features: short palpebral fissures (<2 SD below mean), flattened philtrum, thin upper lip (having all 3 features is highly specific for alcohol exposure
  - neurodevelopmental dysfunction (need ≥3): motor skills; neuroanatomy/neurophysiology; cognition; language; academic achievement; memory; attention; executive function (impulse control and hyperactivity); affect regulation; adaptive behaviour, social skills or social communication, or microcephaly in infant and young children
- diagnosis of ARBD and ARND require evidence of maternal alcohol consumption during pregnancy
- criteria for diagnosis of ARBD
  - congenital anomalies; malformations and dysplasias of the cardiac, skeletal, renal, ocular, and auditory systems
- criteria for diagnosis of ARND
  - complex pattern of behavioural or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone
  - cannot be definitively diagnosed in children <3 yr

Management
- early diagnosis is essential to prevent secondary disabilities by early connection to therapies and supports
- no cure, but individuals with FASD and their families should be linked to community resources and services to improve outcomes
- growth/diet should be monitored closely as nutritional deficiencies are common

Prognosis
- secondary disabilities include unemployment, mental health problems, difficulties with the law, inappropriate sexual behaviour, disrupted school experience, peer problems
- prognosis may be improved if diagnosed before age 6, social and educational supports available, and nurturing living environment

Autism Spectrum Disorder

- prevalence: 1 in 36 children (aged 8 years) diagnosed with ASD (M:F=4:1)

Diagnosis
- persistent deficits in social communication and interaction, manifested in three areas:
  - social-emotional reciprocity: abnormal social approach and failure of normal back-and-forth conversation; reduced sharing of interests, emotions, or affect; failure to initiate or respond to social interactions
  - nonverbal communicative behaviours: poorly integrated verbal and nonverbal communication; abnormalities in eye contact and body language or deficits in understanding and use of gestures; total lack of facial expressions and nonverbal communication
  - developing, maintaining, and understanding relationships: difficulties adjusting behaviour to suit various social contexts; difficulties in sharing imaginative play or in making friends; absence of interest in peers
- restricted, repetitive patterns of behaviour, interests, or activities manifested by ≥2 of: stereotyped or repetitive motor movements, insistence on sameness, highly restricted fixated interests, hyper-/hypo-reactivity to sensory input
- symptoms must be present in early developmental period
- symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
- not better explained by intellectual disability or global developmental delay
- specifiers
  - current severity: requiring very substantial support, requiring substantial support, requiring support
  - ± language impairment, ± intellectual impairment, ± catatonia
  - associated with known medical or genetic condition or environmental factor

Differential Diagnosis
- neurodevelopmental: global delay, intellectual disability, language disorder, social communication disorder, learning disorder, developmental coordination disorder, stereotypic movement disorder
- mental and behavioural: ADHD, mood disorder, anxiety disorder, selective mutism, attachment disorder, ODD, conduct disorder, OCD, childhood schizophrenia
- conditions with developmental regression: Rett syndrome, epileptic encephalopathy (Landau-Kleffner)
- other: hearing/visual impairment, abuse

Treatment
- team-based: school, psychologist, occupational therapist, physiotherapist, speech-language pathologist, pediatrics, psychiatry
- psychosocial: family education and support, school programming, behavioural therapy, social skills training
- treat concomitant disorders such as ADHD, tics, OCD, anxiety, depression, and seizure disorder
- adjunctive pharmacotherapy (does not treat ASD itself): atypical antipsychotics (for irritability, aggression, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated inattention and hyperactivity)

Prognosis
- variable, but improves with early intervention

Attention Deficit Hyperactivity Disorder

- prevalence: 5-12% of school-aged children; M:F=4:1, although girls may be under-diagnosed
- girls tend to have inattentive symptoms; boys tend to have impulsive/hyperactive symptoms

Etiology
- genetic: 75% heritability, dopamine candidate genes DAT1, DRD4
- neurobiology: decreased catecholamine transmission, low prefrontal cortex (PFC) activity, increased β activity on EEG
- cognitive: developmental disability, poor inhibitory control, and other errors of executive function

Diagnosis
- diagnosis requires: onset before age 12, persistent symptoms ≥6 mo, symptoms present in ≥2 settings (i.e. home, school, work), interferes with academic, family, and social functioning, and is divided into 3 subtypes
  - combined type: ≥6 symptoms of inattention and ≥6 symptoms of hyperactivity-impulsivity
  - predominantly inattentive type: ≥6 symptoms of inattention
  - predominantly hyperactive-impulsive type: ≥6 symptoms of hyperactivity-impulsivity
  - for older adolescents and adults (≥ age 17), ≥5 symptoms required
- does not occur exclusively during the course of another psychiatric disorder
- DDx: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (fetal alcohol syndrome, Fragile X syndrome), lead poisoning, history of head injury, traumatic life events (abuse)
- specify current severity (mild/moderate/severe); if in partial remission (past diagnosis, has not met full criteria >6 mo, still functional impairment present)

Table 18. Core Symptoms of ADHD (DSM-5)

Inattention	Hyperactivity	Impulsivity
Careless mistakes	Fidgets, squirms in seat	Blurts out answers before questions completed
Cannot sustain attention in tasks or play	Leaves seat when expected to remain seated	Difficulty awaiting turn
Does not listen when spoken to directly	Runs and climbs excessively	Interrupts/intrudes on others
Fails to complete tasks	Cannot play quietly	
Disorganized	"On the go", driven by a motor	
Avoids and/or dislikes tasks that require sustained mental effort	Talks excessively	
Loses things necessary for tasks or activities		
Distractible		
Forgetful		

Clinical Features
- difficult to differentiate from highly variable normative behaviour before age 4, but often identified upon school entry
- present across multiple settings (i.e. school, home, extracurriculars)
- rule out developmental delay, sensory impairments, genetic syndromes, encephalopathies, or toxins (alcohol, lead)
- increased risk of substance use disorder, depression, anxiety, academic failure, poor social skills, comorbid CD and/or ODD, adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics

Comparative Efficacy and Tolerability of Medications for Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults: A Systematic Review and Network Meta-Analysis
Lancet 2018;5:727-738
Purpose: Estimate the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults.
Methods: Review of double-blind RCTs comparing amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo.
Conclusions: Taking into account both efficacy and safety, evidence from this meta-analysis supports methylphenidate in children and adolescents, and amphetamines in adults, as preferred first-choice medications for the short-term treatment of ADHD.

Treatment
- non-pharmacological: psychoeducation, behavioural management (e.g. parent training, classroom management, social skills training)
- pharmacological: 1st line: stimulants (methylphenidate, amphetamines); 2nd line: atomoxetine and guanfacine XR; 3rd line: clonidine, bupropion, imipramine
- for comorbid symptoms: antidepressants, antipsychotics
- psychosocial intervention is first line for children <6, whereas psychosocial intervention plus medication is considered first line for children ≥6

Contrary to the concerns of many parents and health care providers, treatment with stimulant medications of ADHD in childhood does not increase the likelihood of substance misuse later in life

Prognosis
- 70-80% continue into adolescence, but hyperactive symptoms usually abate
- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable

Motor Delay

- see *Cerebral Palsy, P87* and Medical Genetics, *Duchenne Muscular Dystrophy*, MG8

Endocrinology

Antidiuretic Hormone

Diabetes Insipidus
- see Endocrinology, E22 and Nephrology, NP12

Syndrome of Inappropriate Antidiuretic Hormone
- see Endocrinology, E22 and Nephrology, NP11

Diabetes Mellitus

DIABETES MELLITUS TYPE 1
- see Endocrinology, E7

Epidemiology
- most common form of DM in children, M=F
- variable prevalence internationally, affects 32 in 100000 children in Canada
- can present at any age, but bimodal peaks at 5-9 y/o and at 10-14 y/o

Clinical Features
- can present with polyuria (may manifest as nocturia or secondary enuresis), polydipsia, weight loss (lack of insulin leading to a catabolic state), polyphagia, perineal candidiasis (younger children), visual disturbances, and DKA (30%, with greater incidence in younger children)

Management
- Cornerstone of treatment: family-centred pediatric multidisciplinary team able to provide education and support surrounding survival skills, meal plans, and insulin injections
- Lifestyle factors:
  - diet with consistent levels of carbohydrates, avoiding foods with high glycemic index
  - ~60 min aerobic exercise daily, extensive activity may cause prolonged hypoglycemia or hyperglycemia
  - blood glucoses monitoring (children are more susceptible to hypoglycemia)
- Prevent complications:
  - screen for micro- and macrovascular complications (regular ophthalmology assessments, microalbuminuria, diabetic foot exam), concurrent autoimmune diseases (thyroiditis, celiac disease, etc.), mental health issues (depression, eating disorders, etc.), HTN, dyslipidemia
  - Administer routine immunizations and annual influenza vaccine
- Treat hypoglycemia (lethargy, unusual behaviour, tremor, pallor, tachycardia, diaphoresis, seizure, coma):
  - for mild: administer simple PO carbohydrate (i.e. sweetened fruit juice)
  - for severe: administer IM glucagon or IV dextrose

Diagnostic Criteria for DM (Types 1 and 2) in Children
1. Symptoms (polyuria, polydipsia, weight loss, etc.) and hyperglycemia (Random glucose ≥11.1 mmol/L)
OR
2. Two of the following on one occasion:
- Fasting glucose ≥7.0 mmol/L
- 2 h plasma glucose during OGTT ≥11.1 mmol/L
- HbA1c ≥6.5%

OR
- 3. One of the following on two separate occasions*
- Fasting glucose ≥7.0 mmol/L
- 2 h plasma glucose during OGTT ≥11.1 mmol/L
- HbA1c ≥6.5%

*HbA1c is not recommended as the sole diagnostic test in children and adolescents
* HbA1c has reduced reliability when hemoglobinopathies or increased RBC turnover (i.e. G6PD) present

Blood Glucose Targets
Current Diabetes Canada guidelines recommend an HbA1c target of <7% for children with Type 2 diabetes, with a less stringent target of <7.5% for children with Type 1 Diabetes to minimize hypoglycemia.

Prognosis
- no cure currently
- short-term complications
  - hypoglycemia
    - due to missed/delayed meals, excess insulin or exercise, illness, alcohol ingestion, psychosocial factors
    - can lead to seizures and/or coma as well as permanent neurologic complications

- hyperglycemia
  - due to intercurrent illness, carbohydrate-to-insulin mismatch
  - risk of end-organ damage
- DKA: due to missed insulin doses, infection; most common cause of death

• long-term complications
- microvascular: retinopathy, nephropathy, neuropathy
- macrovascular: metabolic syndrome, CVD, CAD, PVD
- increased risk of other autoimmune diseases
- hypertension, dyslipidemia

DIABETIC KETOACIDOSIS (DKA)

•approximately 40% of children with new onset diabetes will have DKA, and 0.5-1% of DKA cases are complicated by cerebral edema
•symptoms: anorexia, nausea/vomiting, abdominal pain
•signs: Kussmaul breathing, tachycardia, reduced skin turgor, drowsiness, lethargy, coma
•warning signs of neurological deterioration: headache, bradycardia, irritability, decreased LOC, incontinence, specific neurological signs
•management with pediatric-specific protocols:
- ABCs, 100% O2, admit, monitor, correct fluid losses (use isotonic fluids)
- administer insulin
  - avoid insulin bolus and delay infusion until 1 h after fluid resuscitation
  - SC insulin if mild DKA; IV infusion if moderate or severe
- normalize glucose level gradually
- frequently monitor BG, electrolytes, fluid ins/outs, neurological status
- ensure maintenance fluids contain potassium, add glucose to fluids once BG reaches specific threshold

•if cerebral edema is suspected, give mannitol, restrict IV fluids, and move to ICU; imaging only after patient is stabilized
• see Endocrinology, E13

DIABETES MELLITUS TYPE 2

• see Family Medicine, FM25 and Endocrinology, E7
•impaired glucose metabolism due to increased peripheral insulin resistance and relative impairment in insulin secretion

Epidemiology

•rare before age 10, but more common in older children/adolescents (mean age of ~14 y/o)
•prevalence is rising mainly due to the increased incidence of childhood obesity
•risk factors: first or second degree relative with type 2 diabetes, high risk ethnic group, obesity, impaired glucose tolerance, polycystic ovarian syndrome (PCOS), exposure to diabetes in utero, acanthosis nigricans, hypertension, dyslipidemia, non-alcoholic fatty liver disease, atypical antipsychotic medications (see Endocrinology, E7)
- risk reduced with breastfeeding

See Landmark Pediatric Trials table for more information on TODAY, which details the efficacy of three treatments aimed at achieving durable glycemic control in children and adolescents with recent-onset type 2 diabetes.

See Landmark Pediatric Trials table for more information on ELLIPSE, which details the safety and effectiveness of liraglutide and metformin combined therapy for youth with type 2 diabetes.

Clinical Features

•clinical features may be similar to that of T1DM, though most children are asymptomatic (~40%)
- may present in DKA or hyperglycemic hyperosmotic nonketotic state

•screening at least every 3 yr recommended in overweight or obese asymptomatic children after puberty or >10 y/o if ≥1 risk factors
•screening and diagnostic investigations – fasting plasma glucose recommended, 2 h oral glucose tolerance test (higher detection in severe obesity, BMI >99th percentile, and with multiple risk factors), HbA1c
•consider pancreatic autoantibodies (anti-glutamate decarboxylase, anti-islet and anti-insulin antibodies) to exclude T1DM as 10-20% of children with clinical T2DM diagnosis may have T1DM

Management

•initial therapy with insulin used for severe metabolic decompensation at diagnosis (DKA, HbA1c >9%), can wean off
•initiate lifestyle modification program, including diet, weight loss, physical activity (moderate to vigorous activity for at least 60 min/d; screen time less than 2 h/d)
•if glycemic targets not achieved within 3-6 mo from diagnosis with lifestyle intervention alone, either metformin (first line), glimepiride, or insulin should be initiated
- metformin can be initiated at diagnosis if HbA1c >7%

•if glycemic target not met with metformin, add liraglutide with/without basal insulin (especially if severe hyperglycemia – HbA1c >8.5%)
•monitor HbA1c every 3 mo
•advise patient to monitor finger-stick blood glucose levels if on medication with risk of hypoglycemia, are changing medication regimen, have not met treatment goals, or have intercurrent illness
• screening – same as T1DM plus annual screening for PCOS and nonalcoholic fatty liver disease (NAFLD)

Prognosis

•includes microvascular and macrovascular complications similar to T1DM

Growth

• see *Failure to Thrive, P13*

SHORT STATURE

Definition

• short stature: height <3rd percentile
• poor growth evidenced by growth deceleration (height crosses major percentile lines, decreased growth velocity

Epidemiology

• ~2.5% of the population by definition

Etiology

• ABCDEFG (see *Short Stature DDx Memory Aid*)
  ▪ Pathologic short stature (if reduced growth velocity)
  ▪ Non-pathologic short stature (if normal growth velocity)

Short Stature DDx

ABCDEFG
Alone (neglected infant)
Bone dysplasias (rickets, scoliosis, mucopolysaccharidoses, achondroplasia)
Chromosomal (Turner, Down)
Delayed growth (CDGP)
Endocrine (hypopituitary, low GH, **C**ushing, hypothyroid)
Familial (familial short stature)
GI malabsorption (celiac, Crohn's)

Assessment

• history and physical exam
  ▪ family history of growth and pubertal onset
  ▪ plot on growth curve (special growth charts available for Turner syndrome, achondroplasia, DS, and other genetic syndromes)
    ◆ decreased growth velocity often more worrisome than actual height
  ▪ assess for dysmorphic features, disproportionate short stature
  ▪ assess for headaches, vision changes, stigmata of endocrine abnormalities
  ▪ risk factors for GH deficiency: previous head trauma, history of intracranial bleed or infection, head surgery or irradiation, positive family history, breech delivery
• investigations
  ▪ calculate mid-parental height: children are usually in a percentile between their parents' height
    ◆ mid-parental height male = (mother + father's height in cm + 12.5 cm)/2
    ◆ mid-parental height female = (mother + father's height in cm – 12.5 cm)/2
    ◆ likely low mid-parental height in familial short stature (FSS)
  ▪ AP x-ray of left hand and wrist for bone age
    ◆ Constitutional delay of growth and puberty (CDGP) may be distinguished from FSS based upon delayed bone age
  ▪ further investigations recommended with severe short stature or decreased growth velocity, guided by history/physical (e.g. endocrine (TSH/T4, GH testing, etc.), chronic illness (e.g. CBC, creatinine, electrolytes, celiac screen, sweat chloride, etc.), genetic (e.g. microarray, karyotype if aneuploidy suspected), etc.

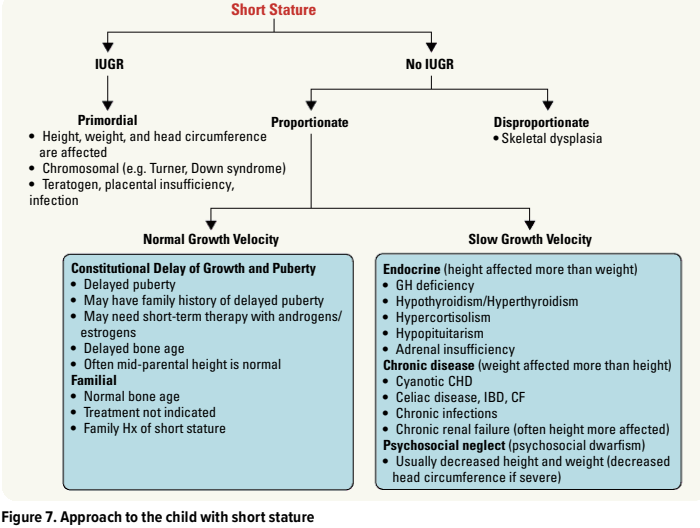
Short Stature
IUGR
No IUGR
Primordial
• Height, weight, and head circumference are affected
• Chromosomal (e.g. Turner, Down syndrome)
• Teratogen, placental insufficiency, infection
Proportionate
Disproportionate
• Skeletal dysplasia
Normal Growth Velocity
Slow Growth Velocity
Constitutional Delay of Growth and Puberty
• Delayed puberty
• May have family history of delayed puberty
• May need short-term therapy with androgens/estrogens
• Delayed bone age
• Often mid-parental height is normal
Familial
• Normal bone age
• Treatment not indicated
• Family Hx of short stature
Endocrine (height affected more than weight)
• GH deficiency
• Hypothyroidism/Hyperthyroidism
• Hypercortisolism
• Hypopituitarism
• Adrenal insufficiency
Chronic disease (weight affected more than height)
• Cyanotic CHD
• Celiac disease, IBD, CF
• Chronic infections
• Chronic renal failure (often height more affected)
Psychosocial neglect (psychosocial dwarfism)
• Usually decreased height and weight (decreased head circumference if severe)

Figure 7. Approach to the child with short stature

Management
- depends on etiology and severity of problem as perceived by parents/child
- no treatment for non-pathological short stature, except for idiopathic short stature (height <3rd percentile without any endocrine, metabolic, or other disease etiology)
- GH therapy for GH deficiency: if administered at an early age, can help patients achieve adult height. Requirements for GH therapy:
  - GH shown to be deficient by 2 different stimulation tests (with arginine, glucagon, insulin)
  - growth velocity <3rd percentile or height <3rd percentile
  - bone age x-rays show unfused epiphyses/delayed bone age
- support and management of resultant self-image issues, social anxiety, etc.

TALL STATURE
- height greater than 2 SDs above the mean for a given age, sex, and race

Etiology
- constitutional/familial
- endocrine: Beckwith-Wiedemann syndrome, hyperthyroidism, hypophyseal gigantism, precocious puberty
- genetic: homocystinuria, Klinefelter syndrome, Marfan syndrome, Sotos syndrome

Hypercalcemia/Hypocalcemia/Rickets

- see Endocrinology, E48

Hyperthyroidism and Hypothyroidism

- may be congenital or acquired (for acquired causes, see Endocrinology, E30)

CONGENITAL HYPERTHYROIDISM
- also known as neonatal Graves' disease

Epidemiology
- ~1 in 25000 neonates, M=F

Etiology
- typically caused by transplacental transfer of TSH receptor antibody (TRAb)
- rare causes include mutations in the TSH receptor pathway

Clinical Features
- history and physical exam
  - maternal history of thyroid pathology and management
  - low birthweight, IUGR, microcephaly, premature birth, tachycardia, irritability, frontal bossing, triangular facies, hepatosplenomegaly, goitre, flushing, sweating

Investigations
- TSH receptor antibody levels during the 3rd trimester or in the cord blood
- neonatal TSH, T3, free T4

Management
- methimazole and β-adrenergic blocker (e.g. propranolol)

Prognosis
- with prompt treatment, hyperthyroidism improves
  - however, long-term cognitive and CNS problems can still occur
- risk for development of central hypothyroidism later in life

CONGENITAL HYPOTHYROIDISM

Epidemiology
- incidence: 1 in 2000-4000 newborn births; F:M=2:1
- one of the most common preventable causes of intellectual disability

Etiology
- may be classified as permanent or transient congenital hypothyroidism (CH)
  - subcategorize into primary (85% thyroid dysgenesis, 15% inborn errors of thyroid gland hormone biosynthesis), secondary/central (pituitary/hypothalamic issue), or peripheral CH (deficits in thyroid hormone transport, metabolism, or action)
- causes of transient hypothyroidism: maternal antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications; neonatal iodine deficiency/excess, congenital liver hemangiomas, certain gene mutations

Clinical Features
- history and physical exam
  - usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  - prolonged jaundice, feeding difficulty, lethargy, constipation, umbilical hernia, macroglossia, large fontanelles, puffy face, swollen eyes, hypotonia (signs/symptoms develop over first few mo)
  - examine for congenital malformations (especially cardiac) and dysmorphic features
  - central hypothyroidism associated with hypoglycemia, micropenis, undescended testes, features of diabetes insipidus
  - most commonly presents as a positive newborn screen result

- Investigations
  - all infants should be screened for primary CH
  - repeat screening at 2 wk for infants at high-risk: preterm, SGA, infants in NICU, specimen collection <24 h of life, multiple births
  - diagnosis through newborn screening of TSH (most sensitive for primary CH) or free T4; abnormal results should be confirmed with serum levels from venipuncture
    - ↑TSH, ↓free T4 in primary CH
    - ↓free, ↓free T4 in secondary CH
  - primary CH (optional): radioisotope scanning/ultrasound of thyroid for severity, serum thyroglobulin, maternal antithyroid antibodies, urinary iodine
  - secondary CH: MRI, gene analysis, eye exam for optic nerve hypoplasia (assess pituitary)

Management
- thyroxine replacement, hormone normalization should be done within 2 wk to avoid cognitive impairment
- counsel against using soy based formulas

Prognosis
- excellent outcome if treatment started within 1-2 mo of birth
- if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or disability (mild to profound), intellectual impairment, poor growth, hearing loss

Disorders of Sexual Development

AMBIGUOUS GENITALIA

Definition
- newborn or child whose sex is difficult to assign based on the appearance of genitalia
- subtype of DSD: a condition in which development of chromosomal, gonadal, or anatomic sex is atypical
- subtypes: 46,XX DSD, 46,XY DSD, ovotesticular DSD (true hermaphrodite)

Epidemiology
- incidence of genital abnormalities at birth is as high as 1 in 300
- prevalence of complex anomalies with true sexual ambiguity much lower at ~1 in 5000

Etiology
- 46,XY DSD
  - inborn error of testosterone biosynthesis or Leydig cell hypoplasia
  - 5-α-reductase deficiency, androgen receptor deficiency or insensitivity
  - LH/hCG unresponsiveness
- 46,XX DSD
  - virilizing CAH (most common)
  - maternal source: virilizing ovarian or adrenal tumours, untreated maternal CAH, placental aromatase deficiency
- ovotesticular DSD
  - both ovarian follicles and seminiferous tubules in the same patient with a 46,XX karyotype
  - mixed gonadal dysgenesis

Risk Factors
- parental consanguinity, positive family history of ambiguous genitalia, early childhood illness/death, or primary amenorrhea, maternal medications during pregnancy (e.g. androgens, progesterones, danazol, phenytoin, aminoglutethimide, endocrine disruptors)

Assessment
- history
  - thorough obstetrical history, including prenatal screens, maternal medications, and maternal virilization in pregnancy
  - family history: autosomal recessive pattern may suggest CAH, X-linked recessive pattern may suggest androgen insensitivity syndrome
- physical exam
  - XY: small phallus, hypospadias, bilateral cryptorchidism (undescended testicles)
  - XX: clitoromegaly, labioscrotal fusion
  - look for concurrent midline defects, dysmorphic features, and congenital abnormalities

- investigations
  - karyotype and genetic workup, including FISH for SRY gene, as indicated
  - blood work: electrolytes and renin (evidence of salt-wasting in CAH); 17-OH-progesterone, androgens, FSH and LH, glucose
  - imaging: abdominal and pelvic U/S to look for gonads, uterus, and vagina

Management
- avoid announcement of probable sex or use of personal pronouns until all tests are complete
- continuous psychosocial support for parents and child during development
- promote individualized management with respect to sex of rearing, surgical intervention, hormonal therapy, and preservation of fertility

CONGENITAL ADRENAL HYPERPLASIA

Definition
- autosomal recessive disorder characterized by a defect in various synthetic enzymes required for cortisol and aldosterone production in the adrenal cortex
  - adrenal cortex normally produces balanced levels of aldosterone, cortisol, and androgens

Epidemiology
- occurs in ~1 in 15000 live births
- most common cause of ambiguous genitalia in genotypically normal females (46,XX)

Etiology
- 21-OH deficiency is responsible for ~95% of CAH cases
- ↓ results in ↓ cortisol and aldosterone production with shunting toward ↑↑ androgens
- cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
- rarer causes include deficiencies in 11-OH, cholesterol desmolase, 17-OH, and 3-HSD

Clinical Features
- depends on which enzyme in cortisol synthesis pathway is defective
- presentation of 21-OH deficiency can be divided into:
  - classic deficiency with salt wasting: inadequate aldosterone resulting in FTT, hyperkalemia, hyponatremia, hypoglycemia, acidosis (majority of classic CAH types)
  - classic deficiency without salt wasting: simple virilization with adequate aldosterone levels
    - females typically present with genital ambiguity, amenorrhea, precocious puberty, polycystic ovaries, hirsutism
    - males typically asymptomatic at birth, may show hyperpigmentation (from overproduction of melanocyte stimulating hormone), penile enlargement, rapid growth, and accelerated skeletal maturation; present with signs of virilization later in life
  - non-classic CAH – mild androgen excess, sometimes asymptomatic, precocious puberty and/or virilization present later in life, rarely associated with Addisonian crises (may be indistinguishable from PCOS)
- 21-OH deficiency screening is part of many newborn screening programs across North America (non-classical variant rarely detected)
- high serum levels of 17-OH progesterone in random blood sample diagnostic for 21-OH deficiency
  - assess plasma ACTH, serum electrolytes, plasma glucose, plasma aldosterone, plasma renin activity, blood gas
  - ultrasound – look for enlarged adrenal gland and presence of uterus

Management
- correct any abnormalities in fluids, electrolytes, or serum glucose
- provide glucocorticoids (e.g. hydrocortisone)/mineralocorticoids (fludrocortisone) to reduce ACTH levels, extra glucocorticoids in times of stress
- psychosocial support

Prognosis
- complications if untreated include virilization, acne, salt wasting, hypotension

NORMAL PUBERTAL DEVELOPMENT

Physiology
- puberty occurs with the maturation of the HPG axis
- ↑ pulsatile release of GnRH → ↑ release of LH and FSH → maturation of gonads, release of sex steroids → secondary sexual characteristics
- adrenal production of androgens also required

Females
- onset: ages 8-13 (may start as early as 7 in girls of African descent)
- usual sequence
  1. thelarche: breast budding
  2. pubarche: axillary hair, body odour, mild acne
  3. growth spurt
  4. menarche: mean age 12.5 yr; indicates that growth spurt is almost complete; menses may be irregular in duration and length of cycle
- early puberty is common and often constitutional, late puberty is rare (rule out organic causes)

Males
- onset: ages 9-14
- usual sequence
  1. testicular enlargement
  2. penile enlargement
  3. pubarche: axillary and facial hair, body odour, mild acne
  4. growth spurt: occurs later in boys
- early puberty is uncommon (rule out organic causes), late puberty is common and often constitutional
- gynecomastia (transient development of breast tissue) is a common self-limited condition seen in 50% of males during puberty (but any discharge from nipple or fixed mass should be investigated)

Maturity Rating (formerly Tanner Staging)
- scale used in pediatrics that defines physical measurements of development based on external primary and secondary sex characteristics

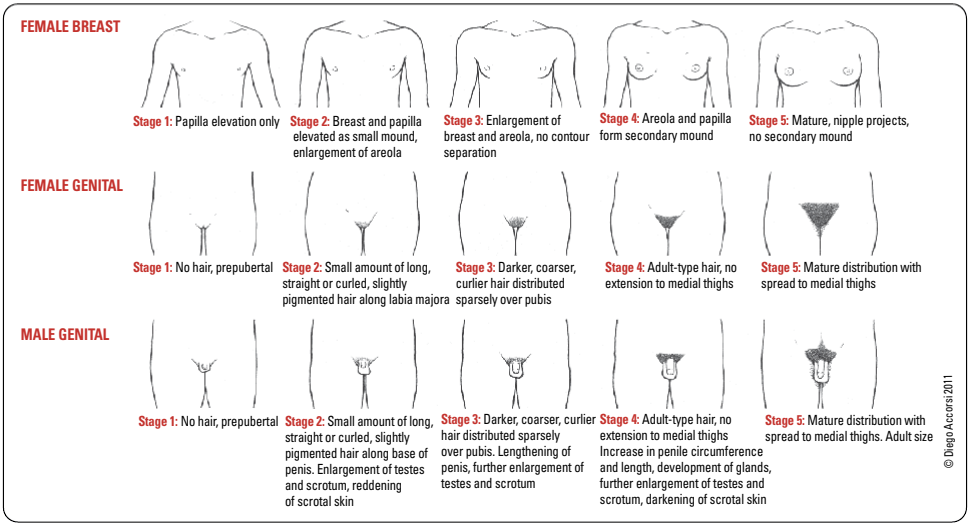
FEMALE BREAST
Stage 1: Papilla elevation only
Stage 2: Breast and papilla elevated as small mound, enlargement of areola
Stage 3: Enlargement of breast and areola, no contour separation
Stage 4: Areola and papilla form secondary mound
Stage 5: Mature, nipple projects, no secondary mound
FEMALE GENITAL
Stage 1: No hair, prepubertal
Stage 2: Small amount of long, straight or curled, slightly pigmented hair along labia majora
Stage 3: Darker, coarser, curlier hair distributed sparsely over pubis
Stage 4: Adult-type hair, no extension to medial thighs
Stage 5: Mature distribution with spread to medial thighs
MALE GENITAL
Stage 1: No hair, prepubertal
Stage 2: Small amount of long, straight or curled, slightly pigmented hair along base of penis. Enlargement of testes and scrotum, reddening of scrotal skin
Stage 3: Darker, coarser, curlier hair distributed sparsely over pubis. Lengthening of penis, further enlargement of testes and scrotum
Stage 4: Adult-type hair, no extension to medial thighs Increase in penile circumference and length, development of glands, further enlargement of testes and scrotum, darkening of scrotal skin
Stage 5: Mature distribution with spread to medial thighs. Adult size
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Figure 8. Tanner staging

PRECOCIOUS PUBERTY

Definition
- development of secondary sexual characteristics 2-2.5 SDs before population mean
- <8 yr for females, <9 yr for males

Epidemiology
- 1 in 10000; F>M

Etiology
- usually idiopathic in females (90%), more suggestive of pathology in males (50%)
- central (GnRH dependent)
  - hypergonadotropic hypergonadism; hormone levels as in normal puberty
  - premature activation of the HPG axis
  - differential diagnosis: idiopathic or constitutional (most common in females), obesity, CNS disturbances (tumours, hamartomas, post-meningitis, increased ICP, radiotherapy), NF, primary severe hypothyroidism
- peripheral (GnRH independent)
  - hypogonadotropic hypergonadism
- differential diagnosis
    - males: testicular tumour, gonadotropin/hCG secreting tumour (hepatoblastoma, intracranial teratoma, germinoma)
    - females: ovarian cysts/tumours
    - both: adrenal disorders (CAH, adrenal neoplasm), exogenous steroid administration, McCune-Albright syndrome, aromatase excess syndrome, rarely primary hypothyroidism (Van Wyk-Grumbach syndrome)

Assessment
- history
  - symptoms of puberty, family history of precocious puberty, medical illness
- physical exam

- growth velocity
  - prepubertal: minimum 4 cm/yr
  - growth spurt: males 10-14 cm/yr, females 8-12 cm/yr
  - complete physical exam, including Tanner staging and neurological assessment
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, DHEA-S, 17-OH-progesterone, prolactin)
  - secondary tests: MRI head, pelvic U/S, β-hCG, GnRH, and/or ACTH stimulation test

A child (generally boys and girls <6/7 y/o) with proven central precocious puberty should receive an MRI of the brain

Management
- indications for medical intervention to delay progression of puberty: rapid advancement of puberty, early age, risk of compromise of final adult height, psychological
- central causes: goals are to preserve height and alleviate psychosocial stress; GnRH agonists (e.g. leuprolide) most effective
- peripheral causes: goal is to limit effects of elevated sex steroids; medications that decrease the production of a specific sex steroid or block its effects (e.g. ketoconazole, spironolactone, tamoxifen, anastrozole); surgical intervention

DELAYED PUBERTY

Definition
- failure to develop secondary sex characteristics by 2-2.5 SDs beyond the population mean
  - for males: lack of testicular enlargement by age 14
  - for females: lack of breast development by age 13 OR absence of menarche by age 16 or within 5 yr of pubertal onset

Epidemiology
- M>F

Etiology
- usually constitutional delay in males, more suggestive of pathology in females
- central causes
  - constitutional delay in activation of HPG axis (most common)
  - hypogonadotropic hypogonadism (e.g. various genetic syndromes (e.g. Kallmann syndrome), hypothalamic/pituitary disorders, chronic illness, hypothyroidism, hyperprolactinemia, poor nutrition, excessive exercise, etc.)
- peripheral causes
  - hypergonadotropic hypogonadism (e.g. primary gonadal failure, gonadal damage, Turner syndrome, Klinefelter syndrome, hormone deficiency, androgen insensitivity syndrome, etc.)

Clinical Features
- weight loss, short stature, family history of puberty onset, medical illness, high performance athletes (females), congenital anomalies, or neurologic symptoms
- assessment and investigations
  - physical exam: growth velocity (see *Precocious Puberty, P38* for normal values)
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, IGF-1), CBC, electrolytes, BUN, Cr, LFTs, liver enzymes, ESR, CRP, IGF-1, urinalysis
  - secondary tests: MRI head, pelvic U/S, karyotype, IBD panel, celiac disease panel, LH levels following GnRH agonist, prolactin

Management
- identify and treat underlying cause
- patients with constitutional delay or GnRH deficiency may be offered "jump start" therapy to induce puberty: cyclic estradiol and progesterone for females, testosterone for males
- refer to pediatric endocrinologist for hormone therapy

Fluids and Electrolytes

Approach to Infant/Child with Dehydration

Etiology
- decreased intake: poor oral intake during acute illness, breastfeeding difficulties, eating disorders
- increased losses: common sites include GI tract e.g. diarrhea, vomiting, bleeding), skin/mucous membranes (fever, burns, hemorrhage, stomatitis), urine (osmotic diuresis (e.g. hyperglycemia, DKA)), diuretic therapy, DI, post-obstructive/post ATN recovery diuresis, and respiratory tract (tachypnea, bronchiolitis, pneumonia)

Management
- if suspect dehydration based on history (acute illness, decreased number of wet diapers, lethargy, changes in mental status, increased thirst, etc.), you must:

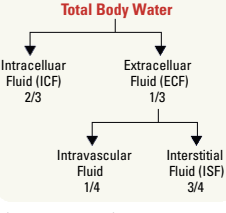


Figure 9. Body fluid compartments

1) Determine degree of extracellular volume contraction

Table 19. Assessment of Degree of Extracellular Volume Contraction Based on Physical Exam

	Mild	Moderate	Severe
<2 yr	5%*	10%*	15%*
>2 yr	3%*	6%*	9%*
Pulse	Normal, full	Rapid	Rapid, weak
Blood Pressure	Normal	Low to normal	Decreased in shock (very late finding in pediatrics and very dangerous)
Urine Output	Decreased	Markedly decreased	Anuria
Oral Mucosa	Slightly dry	Dry	Parched
Anterior Fontanelle	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin Turgor	Normal	Decreased	Tenting
Capillary Refill	Normal (<3 s)	Normal to increased	Increased (>3 s)

* Note that percentages refer to percent loss of pre-illness body weight

Assessment of Severity of Dehydration

C BASE H_2O
Capillary refill
BP
Anterior fontanelle
Skin turgor
Eyes sunken
HR
Oral mucosa
Output of urine

2) Determine the likely electrolyte disturbance

- dependent on etiology of dehydration and type of fluid loss (isotonic vs. hypertonic vs. hypotonic)

Table 20. Electrolyte Content of Various Bodily Fluids

Bodily Fluid	Na^+(mmol/L)	K^+(mmol/L)	Cl^-(mmol/L)	$HCO3^-$(mmol/L)
Saliva	30-80	20	70	30
Gastric Juice	60-80	15	100	0
Pancreatic Juice	140	5-10	60-90	40-100
Bile	140	5-10	100	40
Small Bowel	140	20	100	25-50
Large Bowel	75	30	30	0
Sweat	20-70	5-10	40-60	0

- for moderate and severe dehydration, initial investigations should include urinalysis and blood work examining electrolytes (Na+, K+, Cl-), glucose, acid-base disturbances (blood pH, pCO_2, HCO3–), and impaired renal function (creatinine, BUN)

3) Determine if the child requires PO or IV rehydration

- dehydrated child must receive adequate fluid management, including replacing deficits, ongoing losses, and maintenance fluids
- ORT indication: mild to moderate dehydration
  - advantages: ↓ cost, no IV needed, no increase in incidence of iatrogenic hyper/hyponatremia, parental involvement in therapy
- indications for IV rehydration therapy: severe dehydration requiring close monitoring and frequent assessment of electrolytes, inability to tolerate ORT (e.g. vomiting, alteration in mental status, ileus, monosaccharide malabsorption, etc.), inability to provide ORT, failure of ORT in providing adequate rehydration (e.g. persistent diarrhea or vomiting)

4) Return the child to a normal volume and electrolyte status by replacing current deficits and ongoing losses

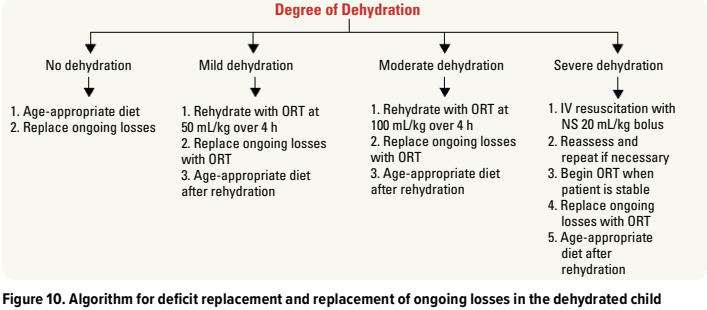

Degree of Dehydration
No dehydration
1. Age-appropriate diet
2. Replace ongoing losses
Mild dehydration
1. Rehydrate with ORT at 50 mL/kg over 4 h
2. Replace ongoing losses with ORT
3. Age-appropriate diet after rehydration
Moderate dehydration
1. Rehydrate with ORT at 100 mL/kg over 4 h
2. Replace ongoing losses with ORT
3. Age-appropriate diet after rehydration
Severe dehydration
1. IV resuscitation with NS 20 mL/kg bolus
2. Reassess and repeat if necessary
3. Begin ORT when patient is stable
4. Replace ongoing losses with ORT
5. Age-appropriate diet after rehydration

Figure 10. Algorithm for deficit replacement and replacement of ongoing losses in the dehydrated child

Special Consideration – SIADH
Clinical Signs: hyponatremia and excretion of concentrated urine
Risk Factors: certain medications (e.g. morphine), postoperative, pain, N/V, pulmonary disease (e.g. pneumonia), CNS disease (e.g. meningitis)
Caution: acute hyponatremia is associated with rapid administration of hypotonic IV fluids, this can lead to cerebral edema and brain herniation or central pontine myelinolysis

5) Provide the appropriate fluid and electrolyte maintenance daily requirements

Table 21. Maintenance Fluid Requirements

Body Weight	100:50:20 Rule (24 h maintenance fluids)	4:2:1 Rule (hourly rate of maintenance fluids)
1-10 kg	100 cc/kg/d	4 cc/kg/h
11-20 kg	1000 cc + 50 cc/kg/d for every kg >10 kg	40 cc + 2 cc/kg/h for every kg >10 kg
>20 kg	1500 cc + 20 cc/kg/d for every kg >20 kg	60 cc + 1 cc/kg/h for every kg >20 kg

- prior to starting IV fluids, serum electrolyte values should be measured
- in children, all maintenance fluids should have a dextrose component due to their higher risk of hypoglycemia, especially if they are NPO
- common IV fluid combinations used in pediatrics:
  - IV normal saline fluid bolus for children with significant hypovolemia
  - for maintenance:
    - newborn: D10W
    - first mo of life: D5W/0.45 NS + KCl 20 mEq/L (only add KCl if voiding well)
    - children without special considerations: D5W/NS + KCl 20 mEq/L – decreased risk of hyponatremia
- most important thing to remember when correcting Na+ aberrations due to fluid deficits
  - risk of cerebral edema with rapid rehydration with hypotonic or isotonic solutions (i.e. NS)
    - therefore replace fluid slowly with close monitoring
    - aim to adjust (increase or decrease) plasma [Na+] by no more than 12 mmol/L/d
- management depends on etiology, severity of symptoms, and timing (acute vs. chronic)

6) Continue to monitor fluid and electrolyte status

- accurate monitoring of daily fluid intake (PO and IV) and ongoing losses (urine output, diarrhea, emesis, drains)
- if child receiving >50% of maintenance fluids through IV, serum electrolyte values should be monitored daily and therapy adjusted accordingly
- avoid iatrogenic hyper/hyponatremia, keep the possibility of SIADH in mind (indicated by hyponatremia and concentrated urine)

Gastroenterology

Vomiting

History

- characteristic of emesis (e.g. projectile, bilious, bloody, etc.)
- pattern of emesis (e.g. association with feeds, cyclic, morning, prolonged, positional, etc.)
- associated symptoms (e.g. anorexia, diarrhea, abdominal pain, hematochezia, fever, headache, etc.)
- red flags: bilious or bloody emesis, projectile vomit, abdominal distension and tenderness, high fever, signs of dehydration, worse when lying down
- remember that vomiting without diarrhea is not always gastroenteritis
  - post-tussive vomiting is also common with coughing fits in children

Physical

- vital signs to determine clinical status and hydration state
- abdominal examination for evidence of obstruction or focal tenderness
- neurologic assessment for signs of increased ICP

Investigations

- if child appears well and no worrisome features, often investigation is not required
- CBC, electrolytes, BUN, Cr, amylase, lipase, glucose, liver enzymes, urinalysis done routinely
- in sick child, add: ESR, venous blood gases, C&S (blood, stool), imaging (x-ray, U/S)

Table 22. Common Differential Diagnosis, Associated Findings, and Diagnostic Approach Based on Age

Cause	Suggestive Findings	Diagnostic Approach
NEONATES – NON-BILIOUS		
Tracheoesophageal Fistula	Excessive secretions soon after birth (e.g. drooling, choking, respiratory distress/ pneumonia), inability to feed, cyanosis (esp with feeds), emesis	Inability to advance NG tube, CXR, upper GI series with water-soluble contrast
Pyloric Stenosis	Projectile non-bilious emesis within 30 min after feeding, fatigue, dehydrated, palpable "olive" in RUQ, decreased stools, hunger	CBC, electrolytes, Cr, BUN, ABG (hypokalemic, hypochloremic metabolic alkalosis), U/S of pylorus, upper GI study (if U/S nondiagnostic)
GERD	Fussiness after feeds, spit ups, arching of back, poor weight gain	Empiric trial of acid suppression, pH monitoring study, upper GI study, endoscopy
Sepsis	Fever, lethargy, tachycardia, tachypnea, widening pulse pressure	CBC, PT/PTT, electrolytes, Cr, BUN, LFTs, bilirubin, lactate, urinalysis, cultures (blood, urine, CSF), CXR
Inborn Error of Metabolism	Poor feeding, FTT, jaundice, hepatosplenomegaly, cardiomyopathy, dysmorphia, developmental delay, neurologic manifestations	Electrolytes, ABG (hyponatremic, hyperkalemic metabolic acidosis), lactate, ammonia, LFTs, BUN, Cr, serum glucose, bilirubin, PT/PTT, CBC
NEONATES – BILIOUS		
Intestinal Obstruction – Malrotation with Volvulus, Meconium Ileus, etc.	Bilious emesis, abdominal distension, pain, bloody stool, shock	AXR, upper GI series, contrast enema
Duodenal Atresia/Stenosis	Bilious emesis, abdominal distension, often seen in DS, jaundice, polyhydramnios during pregnancy, hypokalemic, hypochloremic metabolic alkalosis	AXR, upper GI series ('double bubble' sign)
Hirschsprung's Disease	Bilious emesis, abdominal distension, pain, failure to pass stool	AXR, contrast enema, rectal biopsy
Necrotizing Enterocolitis	Premature neonate, bilious emesis, bloody stools, abdominal distension, intolerance of feeds, electrolytes, Cr, BUN, blood culture	AXR, CBC, electrolytes, Cr, BUN, blood culture
CHILDREN AND ADOLESCENTS		
Acute Viral Gastroenteritis	Diarrhea, fever, abdominal discomfort, myalgia, sick contact, recent travel	Generally clinical diagnosis; if severe: CBC, electrolytes, stool studies
Appendicitis	Periumbilical discomfort that later localizes to RLQ, fever, anorexia	Abdominal U/S
Intussusception	Colicky progressive abdominal pain, drawing of legs up to chest, lethargy, bloody "red currant jelly" stool (Triad)	Abdominal U/S, AXR (rule out other etiologies and perforation)
Non-GI Infection (e.g. Meningitis, pyelonephritis, acute otitis media)	Fever, localized findings depending on cause	Cultures (CSF, blood, urine), brain imaging, CXR
Increased ICP	Nocturnal wakening, progressive recurrent headache worse with Valsalva, focal neurologic deficits, gait disturbance	Brain CT without contrast Therapeutic LP in idiopathic intracranial HTN
Toxic Ingestion	Findings vary by substance - toxidrome, often a history of ingestion	Qualitative and sometimes quantitative levels (urine, blood)
Pregnancy	Amenorrhea, morning sickness, bloating, breast tenderness	Urine β-hCG
Cyclic Vomiting	At least 3 self-limited episodes of vomiting lasting 12 h, 7 d between episodes, no organic cause of vomiting	Diagnosis of exclusion

Management
- rehydration (see *Fluids and Electrolytes, P39*)
- treat underlying cause and correct metabolic/electrolyte abnormalities
- antiemetic drugs can be used in older infants, children, and adolescents with severe vomiting: ondansetron, promethazine, prochlorperazine, metoclopramide
- not recommended when unknown etiology or anatomic abnormalities

Gastroesophageal Reflux

Epidemiology
- extremely common in infancy (up to 50%) but rarely causes pathology (i.e. GERD)

Clinical Features
- passage of stomach contents into esophagus, may cause regurgitation or vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<30 mL)
  - should suspect GERD, defined as when gastroesophageal reflux causes troublesome symptoms/ complications:
    - infant: poor weight gain, irritability, sleep disturbance, respiratory symptoms (coughing, choking, wheezing)

- older child/adolescent: abdominal pain/heartburn, dysphagia, asthma, recurrent pneumonia/upper respiratory infections (if aspirating), recurrent otitis media, upper airway symptoms (chronic cough, hoarseness), dental erosions

Investigations
- thriving baby requires no investigation
- GERD generally can be a clinical diagnosis, diagnostic investigations rarely done but may include:
  - upper GI series – assesses anatomy and motility disorder
  - esophageal pH – assesses frequency and duration of acid exposure, not a definitive diagnostic test
  - upper endoscopy and esophageal biopsy – rule out other conditions that mimic GERD symptoms (e.g. eosinophilic esophagitis), assesses GERD-related esophageal injury
- warning signs of associated disorders requiring further investigations: bilious vomiting, GI tract bleeding, forceful vomiting, fever, lethargy, hepatosplenomegaly, bulging fontanelle, micro/macrocephaly, seizures, abdominal tenderness/distension, suspected genetic, metabolic syndrome, or chronic disease

Management
- conservative (infant): thickened feeds, frequent and smaller feeds, elevation of head, changing formula to hydrolyzed protein or amino acid based formula, starting solid foods if age appropriate
  - breastfeeding infants – sequential elimination diet by mother including milk, beef, soy, and egg
- conservative (older children/adolescent): same as adult management
- medical
  - short-term parenteral feeding to enhance weight gain
  - PPI, H2-blocker: decreases gastric acidity, decreases esophageal irritation
    - recommended when failure of conservative measures, moderate – severe disease or biopsy-proven esophagitis
  - D2 antagonist (domperidone, metoclopramide): generally not recommended for GERD, reserved when concurrent gastroparesis
    - acid-suppressants or motility agents not recommended for infants with uncomplicated reflux
- interventional (indicated for failure of medical therapy):
  - Nissen fundoplication
  - insertion of gastrojejunal tube for post-pyloric feeds
- several of these recommendations should be used cautiously in preterm infants given higher risk of NEC

Complications
- esophagitis, oral feeding aversion, poor weight gain, aspiration, strictures, Barrett's esophagus

Tracheoesophageal Fistula

- see General and Thoracic Surgery, GS75

Pyloric Stenosis

- see General and Thoracic Surgery, GS73

Duodenal Atresia

- see General and Thoracic Surgery, GS74

Malrotation of the Intestine

- see General and Thoracic Surgery, GS73

Diarrhea

- definition of diarrhea varies with diet and age (stool normalcy difficult to define in children)
- infants → increase in stool frequency to twice as often per d ; older children → 3+ loose or watery stools/d
- duration: acute: <2 wk; chronic: >2 wk

Diarrhea is defined as an increase in frequency and/or decreased consistency of stools compared to normal

Normal stool volume
Infants: 5-10 g/kg/d
Children: 200 g/d

Pathophysiology
- osmotic: due to non-absorbable solutes in GI tract (e.g. lactose intolerance)
- secretory: increased secretion of Cl^- ions and water in intestinal lumen (e.g. bacterial toxin)
- malabsorption: less time for absorption due to increased motility or fewer villi to absorb (e.g. short bowel syndrome)

History
- frequency, duration, quality of diarrhea
- associated symptoms (e.g. fever, vomiting, abdominal pain, hematochezia)
- recent antibiotic use or travel
- elements of diet

Physical
- vital signs and complete examination to determine clinical status and hydration state

Investigations
- acute diarrhea (well child with non-bloody diarrhea often requires no further investigations)
  - stool for C&S, O&P, electron microscopy for viruses, *C. difficile* toxin, microscopy (leukocytes suggestive of invading pathogen), blood and urine cultures, CBC, electrolytes, BUN, Cr, glucose, abdominal imaging
- chronic diarrhea
  - serial heights, weights, growth percentiles
  - if child growing well and thriving, workup is limited (stool cultures as above, stool reducing substances)
  - red flags: poor growth, chronic rash, bloody diarrhea, vomiting, abdominal distension, other serious infections, hospitalizations for dehydration (require full workup)
    - stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, *C. difficile* toxin, 3 d fecal fat, α-1-antitrypsin clearance, fecal elastase
    - urinalysis, urine culture
    - CBC, differential, ESR/CRP, smear, electrolytes, total protein, albumin, carotene, Ca^{2+}, PO_4^{3-}, Mg^{2+}, Fe, ferritin, folate, fat-soluble vitamins, PTT, INR
    - sweat chloride, celiac screen, thyroid function tests, urine VMA and HVA, HIV test, lead levels
    - CXR, upper GI series and follow-through
    - specialized tests: endoscopy, small bowel biopsy

Differential Diagnosis

Table 23. Differential Diagnosis of Diarrhea

	Infectious			Non-infectious
Acute	**Viral** Rotavirus Norwalk Enteric adenovirus	**Bacterial** *Salmonella* *Campylobacter* *Shigella* Pathogenic *E. coli* *Yersinia* *C. difficile*	**Parasitic** *Giardia lamblia* *Entamoeba histolytica*	Antibiotic-induced Non-specific: associated with systemic infection Hirschsprung's disease Toxin ingestion Primary disaccharidase deficiency Intussusception
Chronic	**0 – 3 mo**	**3 mo – 3 yr**	**3 – 18 yr**	**Uncommon**
No FTT	GI infection	GI infection Toddler's diarrhea	GI infection Lactase deficiency Irritable bowel syndrome	Drug-induced Chronic constipation UTI
FTT	Disaccharidase deficiency, food protein induced allergic proctocolitis (FPIAP) CF Hirschsprung's Disease	Celiac disease	IBD Endocrine (thyrotoxicosis, Addison's) Neoplastic (pheochromocytoma, lymphoma)	Short bowel syndrome Shwachman-Diamond syndrome HIV Autoimmune Enteropathy Eosinophilic Gastroenteritis

Diarrhea Red Flags
Bloody stool, fever, petechiae or purpura, signs of severe dehydration, weight loss/FTT

Common Antibiotics that Can Lead to *C. difficile Infection*
Fluoroquinolones
Clindamycin
Penicillin (broad spectrum)
Cephalosporins (broad spectrum)

Gastroenteritis

History
- non-specific: diarrhea, vomiting, fever, anorexia, headache, myalgias, abdominal cramps
- viral causes most common, bacterial and parasitic agents more common in older children (2-4 yr)
- recent infectious contacts: symptoms usually begin 24-48 h after exposure

Physical Exam
- febrile
- dehydrated: must assess extent (see *Approach to Infant/Child with Dehydration, P39*)

Investigations
- not usually necessary in young children
- CBC, electrolytes, and stool studies may be indicated in severe cases, if IV hydration required or atypical presentation
- stool analysis: leukocytes/erythrocytes suggests bacterial or parasitic etiology

Complications
- viral gastroenteritis usually self-limiting (lasts 3-7 d in most cases)
- adverse effects related to hypovolemia, shock, tissue acidosis, and rapid onset and over-correction of electrolyte imbalances
- death in severe dehydration (rare in developed countries)

Table 24. Gastroenteritis

	Viral Infection	Bacterial Infection
Etiology	Most common cause of gastroenteritis Commonly: rotaviruses (most common), enteric adenovirus, norovirus (typically older children)	*Salmonella, Campylobacter, Shigella, pathogenic E. coli, Yersinia, C. difficile*
Clinical Features	Associated with URTIs Resolves in 3-7 d Slight fever, malaise, vomiting, vague abdominal pain	Severe abdominal pain High fever Bloody diarrhea
Risk Factors	Daycare, young age, sick contacts, immunocompromised Bacterial infection: travel, poorly cooked meat, poorly refrigerated foods, antibiotics	
Management	Prevention and treatment of dehydration most important (see *Approach to Infant/Child with Dehydration, P39*) Early refeeding advisable, with age-appropriate diet upon completion of rehydration Ondansetron for suspected gastroenteritis with mild to moderate dehydration or failed ORT and significant vomiting Antibiotic or antiparasitic therapy when indicated, antidiarrheal medications not indicated Notify Public Health authorities if appropriate Promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission Rotavirus vaccine	

Toddler's Diarrhea

Epidemiology
- most common cause of chronic diarrhea during infancy
- onset between 6-36 mo of age, resolves spontaneously between 2-4 yr

Clinical Features
- diagnosis of exclusion in thriving child
- 4-6 bowel movements per d
- diet history (e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption)
- stool may contain undigested food particles
- excoriated diaper rash

Investigations:
- Height, weight, and growth percentiles
- No routine investigations necessary if child is otherwise well and growing appropriately

Management
- reassurance that it is self-limiting
- **4F**s (adequate **F**ibre, normal **F**luid intake, lower dietary **F**at (35-40%), discourage excess **F**ruit juice)

Lactase Deficiency (Lactose Intolerance)

Clinical Features
- chronic, watery diarrhea and abdominal pain, bloating associated with dairy intake
- primary lactose intolerance: crampy abdominal pain with loose stool (older children, more common in East Asian and African descent)
- secondary lactose intolerance: older infant, persistent diarrhea (decreased lactase production post viral/bacterial infection, celiac disease, or IBD)

Diagnosis
- investigations usually not needed, trial of lactose-free diet
- symptom assessment with validated questionnaire after oral lactose load
- positive breath hydrogen test if >6 yr after oral lactose load with simultaneous symptom assessment
- tests for lactase deficiency: small bowel biopsy, genetic testing
  - demonstration of lactose malabsorption should be combined with assessment of intolerance symptoms

Management
- lactose-free diet
- lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

Irritable Bowel Syndrome

- see Gastroenterology, G26

Celiac Disease

- Gastroenterology, G21 in children: presents at any age, often 6-24 mo with the introduction of gluten in the diet
- poor weight gain, poor appetite, irritability, apathy, rickets, wasted muscles, flat buttocks, rarely distended abdomen
- GI symptoms: N/V, edema, anemia, abdominal pain, diarrhea
- non-GI manifestations: iron-deficiency anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty, behavioural changes
- associated with other autoimmune disorders (e.g. T1DM, thyroid disease)

Celiac disease is associated with an increased prevalence of IgA deficiency. Since tTG is an IgA-detecting test, you must order an accompanying IgA level

A Celiac disease diet must avoid gluten present in "**BROW**" foods
Barley
Rye
Oats (controversial)
Wheat

Cow's Milk Allergy

Pathophysiology

- cow's milk allergy (CMA) may be either an IgE-mediated reaction or a non-IgE mediated reaction, which is further classified as a food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES), or food-protein-induced enteropathy

Clinical Features

- IgE-mediated CMA reactions occur within hours of exposure and are present on the skin (i.e. urticarial, pruritus, etc.), upper and lower resp tract symptoms (i.e. wheeze, cough, etc.), gastrointestinal symptoms (i.e. abdominal pain, nausea/vomiting, diarrhea, etc.)
- non-IgE-mediated CMA reactions occur hours following ingestion, within few mo, presents with:
  - FPIAP: mild diarrhea, small amounts of bloody stools (common in young infant)
  - FPIES: severe vomiting, and diarrhea, anemia, hematochezia
  - food protein-induced enteropathy: FTT, chronic diarrhea, hypoalbuminemia
- up to 50% of children intolerant to cow's milk may be intolerant to soy protein as well

Investigations

- food challenge (gold standard), skin prick test, serum measurement of allergen-specific IgE, patch testing

Management

- IgE-mediated CMA: stop exposure, epinephrine for acute anaphylactic reactions
- non-IgE-mediated CMA: stop, reintroduce milk at 6-8 mo, vast majority (>90%) will outgrow by 1 yr
- casein hydrolysate formula (Nutramigen®, Pregestimil®) or mother may sequentially remove cow's milk protein, all bovine protein, soy protein, legumes (7 d washout), and continue breastfeeding (with adequate calcium and vitamin D intake)

Inflammatory Bowel Disease

- see Gastroenterology, G22

Cystic Fibrosis

- see Respirology, R12

Constipation

•decreased stool frequency (<3 stools/wk) and/or stool fluidity (hard, pellet-like)

FUNCTIONAL CONSTIPATION

•99% of cases of constipation
•Rome IV criteria for infants and toddlers ≤4 y/o:
- ≥2 of the following for at least 1 mo:
  - ≤2 defecations/wk
  - history of excessive stool retention
  - history of large-diameter stools
  - history of painful or hard bowel movements
  - evidence of large fecal mass in rectum
- in toilet-trained children, the following additional criteria may be used:
  - at least 1 episode/wk of incontinence after the acquisition of toileting skills
  - history of large-diameter stools that may obstruct toilet

Pathophysiology

•lack of fibre in diet or change in diet, poor fluid intake, behavioural
- infants: often occurs when introducing cow's milk after breast milk due to high fat and solute content, lower water content
- toddlers/older children: can occur during toilet training, starting school, or due to pain on defecation, leading to withholding of stool
- adolescents: often related to school stressors, anxiety/eating disorders

Management
- education: explanation of mechanism of functional constipation for parents/older children
- clean out: PEG 3350 flakes (1-1.5 g/kg/d, max 100 g/d), picosalax, PEGlyte®
- maintenance: adequate fluid intake (if <6 mo, 150 mL/kg/d), adequate dietary fibre (fruit, vegetables, whole grains), stool softening (PEG 3350, mineral oil), appropriate toilet training technique (dedicated time for defecation: 3-10 min, 1-2 x/d)
- children should be treated for at least 3-6 mo, and should not be weaned from maintenance therapy until they are having regular bowel movements without difficulty
- regular follow-up with ongoing support and encouragement is essential

Complications
- pain retention cycle: anal fissures and pain from withholding passing stool, chronic dilatation ± overflow incontinence

HIRSCHSPRUNG'S DISEASE (Congenital Aganglionic Megacolon)
- see General and Thoracic Surgery, GS74

OTHER ORGANIC DISORDERS CAUSING CONSTIPATION
- endocrine: hypothyroidism, DM, hypercalcemia
- neurologic: spinal cord abnormalities/trauma, NF
- anatomic: bowel obstruction, anus (imperforate, atresia, stenosis, anteriorly displaced)
- drugs: lead, chemotherapy, opioids
- celiac disease
- others

Abdominal Pain

ACUTE ABDOMINAL PAIN

History
- description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
- associated symptoms: N/V, diarrhea, fever

Physical Exam
- abdominal exam, rectal exam, rash

Investigations
- may include CBC, differential, liver enzymes, lipase, bilirubin, creatinine, CRP, glucose, blood gas urinalysis to rule out UTI, β-HCG, abdominal, pelvic, and/or testicular imaging

Table 25. Differential Diagnosis of Acute Abdominal Pain

Gastrointestinal	Hepatobiliary Tract	Genitourinary	Hematologic	Metabolic	Drug and Toxins	Pulmonary	Miscellaneous
Gastroenteritis	Hepatitis	UTI	Sickle cell crisis	Diabetic ketoacidosis	Erythromycin	Pneumonia	Functional pain
Appendicitis	Cholecystitis	Urinary calculi	Henoch-Schönlein purpura	Hypoglycemia Porphyria	Salicylates	Diaphragmatic pleurisy	Infantile colic
Mesenteric Adenitis	Cholelithiasis	Dysmenorrhea	Hemolytic uremic syndrome		Lead poisoning		Pharyngitis
Constipation	Spleen – infarction, rupture	Mittelschmerz			Venoms		Angioneurotic edema
Ileus	Pancreatitis	PID					Mediterranean fever
Abdominal Trauma		Threatened abortion					Neoplasms (i.e. Wilms' tumour, neuroblastoma, etc.)
Intestinal Obstruction (incarcerated hernia, intussusception, volvulus)		Ectopic pregnancy					
Peritonitis		Nephrolithiasis					
Peptic Ulcer		Testicular torsion					
Meckel's Diverticulum		Ovarian torsion					
IBS		Ruptured ovarian cyst					
Food Poisoning		Endometriosis					
Lactose Intolerance		Hematocolpos					

APPENDICITIS
- see General and Thoracic Surgery, GS35
- most common cause of acute abdomen after age 5
- clinical features: low grade fever, abdominal pain, anorexia, N/V (after onset of pain), peritoneal signs (generalized peritonitis is a common presentation in infants/young children)
- treatment: surgical
- complications: perforation (common in young children), abscess

INTUSSUSCEPTION

• telescoping of segment of bowel into distal segment causing ischemia and necrosis

Epidemiology

• 90% idiopathic, children with CF or GJ tube at significantly increased risk; M:F=3:2
• 60% <12 mo, 80-90% before age 2

Pathophysiology

• usual site: ileocecal junction; jejunum in children with GJ tubes
• lead point of telescoping segment may be swollen Peyer's patches, Meckel's diverticulum, polyp, malignancy, bowel wall edema or submucosal bleeding secondary to HSP, structural abnormalities

Clinical Features

• "classic triad" (<15% patients) - abdominal pain, vomiting, red currant jelly stools
• often preceded by URTI
• sudden onset of recurrent, paroxysmal, severe periumbilical pain associated with inconsolable crying and raising legs toward abdomen with pain-free intervals
• later vomiting (may be bilious) and rectal bleeding (late finding)
• shock and dehydration; lethargy may be only presenting symptom

Diagnosis

• air enema: both diagnostic and therapeutic
• AXR, U/S

Management

Ileoileal: often not significant, treatment usually not necessary
Ileocolic:
• air or saline/contrast enema can be therapeutic (reduces intussusception in 75% of cases), reduction under hydrostatic pressure, surgery rarely needed
• recurrence rate 10-15%, need to consider pathologic lead point

Chronic Abdominal Pain

Epidemiology

• prevalence: 10% of school children (peak at 8-10 yr), F>M

Etiology

• organic (<10%)
  ▪ gastrointestinal
    ◆ constipation (cause vs. effect), infectious
    ◆ IBD, esophagitis, peptic ulcer disease, lactose intolerance
    ◆ anatomic anomalies, masses
    ◆ pancreatic, hepatobiliary
    ◆ celiac disease
  ▪ genitourinary causes: recurrent UTI, nephrolithiasis, chronic PID, Mittelschmerz, dysmenorrhea, ovarian cyst, endometriosis
  ▪ neoplastic (Wilms tumour, neuroblastoma)
  ▪ Neurological (migraine, abdominal migraine)
  ▪ Hematological (leukaemia/lymphoma, sickle cell disease, porphyria)
  ▪ Miscellaneous recurrent (recurrent abdominal pain of childhood)
• functional abdominal pain (90%): can be diagnosed when there are no alarming signs or symptoms, physical exam is normal; no further testing is required, unless high suspicion for organic cause
  ▪ alarming symptoms include involuntary weight loss, deceleration of linear growth, GI blood loss, significant vomiting, chronic severe diarrhea, persistent upper or right lower quadrant pain, unexplained fever, family history of IBD
  ▪ can be further subclassified into functional dyspepsia (pain in upper abdomen), irritable bowel syndrome (alternating bowel movements), abdominal migraine (paroxysmal abdominal pain, associated with anorexia, nausea, vomiting, pallor), functional abdominal pain syndrome

Chronic Abdominal Pain

Rule of 3s
3 episodes of severe pain
Child >**3** y/o
Over **3** mo period

Red Flags for Organic Etiology of Chronic Abdominal Pain

Age <5
Fever
Localizes pain away from midline
Anemia
Evidence of GI blood loss
Rash
Pain wakes child at night
Travel history
Prominent vomiting, diarrhea
Weight loss or failure to gain weight
Deceleration in linear growth
Joint pain
Family history of IBD
Abnormal or unexplained physical exam findings

FUNCTIONAL ABDOMINAL PAIN

Clinical Features

• clustering episodes of vague, crampy periumbilical/epigastric pain, vivid pain description
• seldom awakens child from sleep, less common on weekends
• aggravated by exercise, alleviated by rest
• psychological factors related to onset and/or maintenance of pain, school avoidance
• psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
• diagnosis of exclusion

Investigations
- fecal studies (calprotectin, occult blood) and others based on clinical suspicion (e.g. CBC, ESR, urinalysis, imaging, etc.)

Management
- continue to attend school
- manage any emotional or family problems, counselling, CBT
- trial of high fibre diet, or trial of lactose-free diet may be considered
  - medication rarely used, should be for symptom relief – acid reduction therapy for dyspepsia, antispasmodic agents, smooth muscle relaxants for pain, non stimulating laxatives or antidiarrheals for altered bowel pattern
- possible role for amitriptyline or gabapentin
- reassurance

Prognosis
- pain resolves in 30-50% of children within 2-6 wk of diagnosis
- 30-50% of children with functional abdominal pain have functional pain as adults (e.g. IBS)

Abdominal Mass

Table 26. Differential Diagnosis for Abdominal Mass

	Non-malignant	Malignant
Renal (note: 50% of abdominal masses in newborns are renal in origin)	Hydronephrosis Polycystic kidney disease Hamartoma	Nephroblastoma (Wilms' tumour) Renal cell carcinoma
Adrenal		Neuroblastoma
Ovarian	Ovarian cysts	Ovarian tumours
Other	Hepatomegaly/splenomegaly Pyloric stenosis Abdominal hernia Teratoma Fecal impaction	Lymphoma Rhabdomyosarcoma Retroperitoneal sarcoma

Table 27. Renal Etiologies of an Abdominal Mass

Abdominal Mass	Benign or Malignant	Clinical Features	Management
Hydronephrosis	Benign	Usually asymptomatic Urinary tract obstruction Vesicoureteral reflux	Genetic counselling Unilateral hydronephrosis >4 mm in second trimester, a follow-up US scan in third trimester is performed Persistent hydronephrosis >10 mm require postnatal evaluation
Polycystic Kidney Disease	Benign	Progressive renal failure, hypertension, urinary tract infection, concentrating defects, hematuria, nephrolithiasis, flank pain	BP control with ACE inhibitors Dietary sodium restrictions Statins Vasopressin receptor antagonists
Hamartoma	Benign	Asymptomatic abdominal swelling Abdominal pain (30-40%) Hematuria (12-25%) Fever and hypertension (25%)	Surgery, chemotherapy, radiation
Wilm's Tumour	Malignant	Asymptomatic abdominal swelling Abdominal pain (30-40%) Hematuria (12-25%) Fever and hypertension (25%)	Surgery, chemotherapy, radiation
Renal Cell Carcinoma	Malignant	Classic triad of flank pain, hematuria, and palpable abdominal renal mass	For localized RCC, surgery is curative For advanced RCC, immunotherapy and radiation

Upper Gastrointestinal Bleeding

- see Gastroenterology, G28

Lower Gastrointestinal Bleeding

• see Gastroenterology, G30

Etiology
• acute
  - infectious (bacterial, parasitic)
  - antibiotic-induced (C. difficile)
  - NEC in preterm infants
  - anatomic
  - malrotation/volvulus, intussusception
  - Hirschsprung disease
  - Meckel's diverticulitis
  - anal fissures, hemorrhoids
  - vascular/hematologic
  - HSP
  - HUS
  - coagulopathy
• chronic
  - anal fissures (most common)
  - infectious colitis
  - IBD
  - FPIAP
  - allergic (milk protein)
  - structural
  - polyps (most are hamartomas)
  - coagulopathy
  - neoplasms (rare)

Physical Exam
•general exam: hemodynamic status, evidence of poor growth, fever
•anal and rectal exam: tags, fissures, anal fistulas, polyps, foreign body, blood per rectum
• stool appearance
• NG aspirate
•lower GI bleed may present as melena (if it involves the small bowel) or hematochezia

Investigations
•stool cultures (C&S, C. difficile toxin)
• urinalysis and microscopy
•CBC, smear, differential, ESR, CRP, electrolytes, urea, Cr, INR, PTT, albumin, iron studies, amoeba titers
• radiologic investigations
• Meckel's radionuclide scan
• Colonoscopy

Management
•acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
•treatment dictated by etiology
•once stable, endoscopy and/or surgery as indicated

Genetics, Dysmorphisms, and Metabolism

• see Medical Genetics

Hematology

Approach to Anemia

CLASSIFICATION
• mechanism: decreased production (inadequate reticulocyte response) vs. increased destruction or loss (adequate reticulocyte response)
• A "normal" reticulocyte count in the context of anemia would be indicative of an inadequate bone marrow response

Normal Hb Values by Age

Age	Hb Range (g/L)
Newborn	137-201
2 wk	130-200
3 mo	95-145
6 mo-6 yr	105-140
7-12 yr	110-160
Adult female	120-160
Adult male	140-180

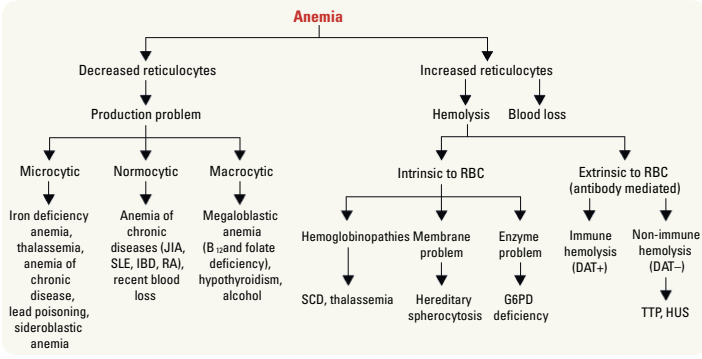


Figure 11. Approach to anemia

Physiologic Anemia

- high Hb (>170 g/L) and reticulocyte count at birth is caused by a relatively hypoxic environment in utero and increased erythropoietin levels
- after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 wk of life, there is virtually no erythropoiesis due to new O_2 rich environment), and increasing blood volume secondary to growth
- lowest levels about 100 g/L at 8-12 wk (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
  - red flags suggesting non-physiologic anemia may include Hb level lower than expected with physiologic anemia, signs of hemolysis, or symptoms of anemia
- usually no treatment required

Mean corpuscular volume (MCV) in childhood varies with age
General rule: lower normal limit of MCV = 70 + age (yr) until 80 fL (adult standard)

Iron Deficiency Anemia

- most common cause of childhood anemia
- full term infants exhaust iron reserves by age 6 mo
- premature infants have lower iron reserves, therefore exhausted by age 2-3 mo if not supplemented
- common diagnosis between 6 mo-3 yr and 11-17 yr due to periods of rapid growth and increased iron requirements; adolescents may also have poor diets and menstrual losses

Always order a CRP with ferritin because ferritin is an acute phase reactant, therefore, normal or high ferritin does not exclude iron deficiency anemia during inflammation (e.g. infection).

Iron deficiency is rare in children <6 mo in the absence of blood loss or low birth weight

Etiology

- children at risk: premature, maternal iron deficiency, LBW, low socioeconomic status (SES), etc.
  - Indigenous communities at much higher risk due to poverty, food insecurity, and diminished access to traditional foods
  - Selective eating increases risk (i.e. Children with autism)
- dietary risk factors: cow's milk in first year of life
  - age >6 mo: <2 servings/d of iron-fortified cereal, red meat, or legumes
  - age <12 mo: use of low-iron formula (<10 mg/L); primary diet of cow, goat, or soy milk
  - age 1-5 yr: >500 ml/d of non-iron fortified milk
- malabsorption syndrome (i.e. celiac disease, Crohn's disease, short bowel syndrome, etc.)
- blood loss
  - iatrogenic: repeated blood sampling (especially in hospitalized neonates)
  - allergic: cow's milk protein-induced colitis
  - gastrointestinal: IBD

Clinical Features

- usually asymptomatic until marked anemia
- symptoms may include: pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur, angular cheilitis, koilonychia (spoon nails)

Investigations

- CBC: low Hb, and MCV, reticulocyte count normal or high (absolute number low)
- Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
  - ratio <13 suggests thalassemia
  - ratio >13 suggests iron deficiency
- blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikilocytosis
- iron studies: low ferritin, other (low iron, high total iron binding capacity, high transferrin, low transferrin saturation)

Prevention
- breastfed term infants: at age of 6 mo ensure ≥2 feeds/d of iron-rich foods, if unable consider iron supplementation
- non-breastfed (<50% of diet) term infants: give iron-fortified formula from birth
- low birth weight (BW) infants:
  - BW of 2.0 - 2.5 kg: iron supplementation of 1-2mg/kg/d for first 6 mo
  - BW <2.0kg: iron supplementation of 2-3 mg/kg/d for first 12 mo
  - for predominantly formula-fed infants: formula high in iron, no supplementation required
- no cow's milk until 12 mo, early introduction of red meat and iron-rich vegetables: total daily iron should be 11 mg (ages 6-12 mo), 7 mg (ages 1-3 yr)
- consider screening Hb levels in infants not receiving iron-fortified formula at 9-12 mo, and earlier if other risk factors present

Management
- encourage diverse, balanced diet, limit homogenized milk to 500 mL/d (ideally after meals)
- oral iron therapy: 4-6 mg/kg/d elemental iron, divided BID to TID, for 3-6 mo to replenish iron stores
  - increased reticulocyte count in 2-3 d (peaks d 5-7)
  - increased hemoglobin by 30 d
  - repletion of iron stores in 1-3 mo
  - repeat hemoglobin levels after 1 mo of treatment
- poor response to oral iron therapy: non-adherence, medication intolerance, ongoing blood loss, IBD, celiac disease, incorrect diagnosis
  - Emerging evidence for IV iron sucrose use (especially if there are concerns about adherence)

Complications
- can cause irreversible effects on development if untreated (behavioural and intellectual deficiencies)
- angular cheilitis, glossitis, koilonychia (spoon nails)

Anemia of Chronic Disease

- see Hematology, H16

Sickle Cell Disease

- see Hematology, H21

Thalassemia

- see Hematology, H19

Hereditary Spherocytosis

- see Hematology, H24

Glucose-6-Phosphate Dehydrogenase Deficiency

- see Hematology, H24

G6PD deficiency protects against parasitism of RBCs (i.e. malaria)

Bleeding Disorders

- see Hematology, H28

Table 28. Evaluation of Abnormal Bruising/Bleeding

	PFA	PT	PTT	VIII:C	VWF	Platelets	Fibrinogen
Hemophilia A	N	N	↑	↓	N	N	N
Hemophilia B	N	N	↑	N	N	N	N
von Willebrand Disease	↑	N	N or ↑	↓	N or ↓	N	N
DIC	N or ↑	↑	↑	↓	N	↓	↓
Vitamin K Deficiency	N	↑	↑	N	N	N	N
Thrombocytopenia	↑	N	N	N	N	↓	N

N=normal; DIC = disseminated intravascular coagulation; PFA = platelet function assay; VIII:C = Factor VIII coagulant activity; VWF = von Willebrand Factor

Extensive bruising in the absence of lab abnormalities: should raise consideration of child maltreatment

Vitamin K Deficiency

Etiology
- most commonly in infants <6 mo due to hepatic immaturity not efficiently utilizing vitamin K (in preterm infants), having poor vitamin K stores, and low vitamin K content in milk, leading to vitamin K deficiency bleeding (VKDB) previously known as hemorrhagic disease of the newborn (HDNB)
- non-classic presentation acquired later in life, often in association with chronic malabsorption (i.e. CF, celiac disease, IBD, biliary atresia, primary biliary cholangitis, primary sclerosing cholangitis, etc.), liver failure, medications (i.e. antibiotics)
  - risk factors for non-classic presentation: maternal medication (i.e. antiepileptic drugs), chronic malabsorption, no prophylaxis

Clinical Features
- VKDB due to relative deficiencies of vitamin K-dependent coagulation factors
  - generalized bleeding; cutaneous bleeding, mucosal bleeding (GI, umbilicus), and/or intracranial hemorrhage
  - early-onset (in first 24 h), classic (27 d), and late-onset (2-12 wk up to 7 mo, high occurrence of ICH)
- acquired vitamin K deficiency symptoms may include: easy bruising, mucosal bleeding (i.e. epistaxis, GI bleed, hematuria, etc.)

Management
- VKDB managed urgently with IV/SC vitamin K (1-2 mg). If there is severe bleeding, also administer fresh frozen plasma or prothrombin complex concentrate
- prevented with vitamin K IM injection (0.5-1 mg) at birth, can also be given orally as vitamin K (doses: first feed, 1, 4, 8 wk) for breastfed, term infants but higher risk of VKDB
- bleeding due to vitamin K deficiency of other acquired etiologies managed with PO/IM/SC/IV vitamin K, with dose dependent on condition

Immune Thrombocytopenic Purpura

Definition
- ITP is isolated thrombocytopenia (platelet count <100000/μL with normal white blood cell count and hemoglobin)

Epidemiology
- most common cause of symptomatic thrombocytopenia in childhood
- peak age: 2-5 yr, M>F (slightly)
- incidence 5 in 100000 children per yr

Etiology
- caused by autoantibodies that bind to platelet membranes → Fc-receptor mediated splenic uptake → destruction of platelets

Clinical Features
- 60% present within 1 mo after viral illness (e.g. URTI, chicken pox)
- sudden onset of petechiae, purpura, bleeding in an otherwise well child
- clinically significant bleed in only 3% (severe bleed more likely with platelet count <10) with <0.5% risk of intracranial bleed
- no lymphadenopathy, no hepatosplenomegaly

Investigations
- diagnosis made in well appearing patients with mucocutaneous bleeding without other systemic symptoms or signs and lab confirmation of ITP (diagnosis of exclusion)
- labs: thrombocytopenia with normal RBC, WBC
- bone marrow aspirate only indicated if red flags on history, exam, or lab studies (not needed in initiation of corticosteroid treatment or before splenectomy)
- differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), immunodeficiency syndromes, autoimmune (SLE, autoimmune lymphoproliferative syndrome, autoimmune hemolytic anemia)
- testing for antinuclear antibodies not needed in a typical case of presumed ITP

Management
- involve family in management; shared decision-making
- no or mild bleeding (i.e. only bruising/petechiae) – consider watchful waiting (irrespective of platelet levels)
- moderate bleeding (i.e. severe skin manifestations with some mucosal lesions and some troublesome epistaxis or menorrhagia) – IVIg (1 g/kg) or steroids; if Rh-positive or DAT-negative can use anti-D (not indicated in low Hb from blood loss or autoimmune hemolysis)
- severe (i.e. prolonged epistaxis, GI bleeding, or intracranial hemorrhage) - immediate treatment with IV steroids and IVIg; may use tranexamic acid as adjunct therapy

- treatment with IVIg or prednisone if mucosal or internal bleeding, platelets <10, or at risk of significant bleeding (surgery, dental procedure, concomitant vasculitis, or coagulopathy)
- IVIg = faster increase in platelet count
- life-threatening bleed: additional platelet transfusion ± emergency splenectomy
- persistent (>3-12 mo) or chronic (>12 mo): re-evaluate; treat if symptoms persist
- supportive: avoid contact sports and ASA/NSAIDs

Hemophilia

- see Hematology, H32

von Willebrand's Disease

- see Hematology, H30

Oncology

- cancer is the second most common cause of death after injuries in children >1 yr
- cause is rarely known, but increased risk for children with: chromosomal syndromes (e.g. Trisomy 21), cancer predisposition syndromes (e.g. Li-Fraumeni syndrome), prior malignancies, neurocutaneous syndromes, immunodeficiency syndromes, family history, exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (30%), followed by brain tumours (25%) and lymphomas (15%)
- some malignancies are more prevalent in certain age groups
  - newborns: neuroblastoma, Wilms' tumour, retinoblastoma
  - infancy and childhood: leukemia, neuroblastoma, CNS tumours, Wilms' tumour, retinoblastoma
  - adolescence: lymphoma, leukemia, gonadal tumours, germ cell tumours, thyroid cancers, melanoma, bone tumours
- unique treatment considerations in pediatrics because radiation, chemotherapy, and surgery can impact growth and development, endocrine function, and fertility
- good prognosis: treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers (>80%)

Most common cause of acute bilateral cervical lymphadenopathy is viral illness

Lymphadenopathy

Definition

- Swelling of the lymph nodes; can present as either localized or diffuse, and malignant or benign

Clinical Features

- features of malignant lymphadenopathy: firm, discrete (not often), non-tender, enlarging, immobile, worrisome location (i.e. supraclavicular or generalized), abnormal imaging findings or bloodwork, constitutional symptoms
- fluctuance, warmth, or tenderness are more suggestive of benign nodes (infection)

Differential Diagnosis

- infection
  - viral: URTI, EBV, CMV, adenovirus, HIV, measles, mumps, rubella, Hep B
  - bacterial: S. aureus, GAS, anaerobes, Mycobacterium (e.g. typical and atypical TB), cat scratch disease (Bartonella), Rickettsia
  - other: fungal, protozoan
- autoimmune: rheumatoid arthritis, SLE, serum sickness
- malignancy: lymphoma, leukemia, metastatic solid tumours
- storage diseases: Niemann-Pick, Gaucher
- other: sarcoidosis, Kawasaki disease, histiocytosis

Investigations

- assess location, size, consistency, fixation, and tenderness of each node
- generalized lymphadenopathy (≥2 body areas)
  - CBC and differential, blood culture
  - inflammatory markers (ESR, CRP)
  - serology: EBV, CMV and others as indicated by history and physical exam (e.g. HIV, fungal, toxoplasmosis)
  - uric acid, LDH, electrolytes
  - CXR
  - tuberculin skin test
  - if indicated other blood work i.e. inflammatory panel (ANA, RF, dsDNA)
  - biopsy: late biopsy (within 4 wk) if increasing in size, or >2 cm and unclear diagnosis or no response to treatment. Do early biopsy if supraclavicular nodes, nodes >4 cm, or groups of nodes with total diameter >3 cm

- regional lymphadenopathy (1 body area)
  - period of observation if asymptomatic
  - trial of oral antibiotics
  - ultrasound
  - biopsy (especially if persistent >4 wk and/or constitutional symptoms)
  - if supraclavicular lymphadenopathy: CXR to rule out mediastinal mass

Leukemia

- see Hematology, H46

Definition
- leukemia is a cancer that starts in the bone-forming tissue (e.g. bone marrow), causing abnormal blood cell production

Epidemiology
- mean age of diagnosis 2-5 yr but can occur at any age
- most commonly diagnosed cancer in children aged 0-14 yr
- heterogeneous group of diseases
  - ALL (80%)
  - AML (15%)
  - CML (<5%)
  - CLL (<1%)
- children with DS are 15 times more likely to develop leukemia

Clinical Features
- infiltration of leukemic cells into bone marrow results in bone pain and bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in lymphadenopathy, hepatosplenomegaly, CNS manifestations, testicular disease
- fever, fatigue, weight loss, bruising, bone pain, and easy bleeding
- investigations: CBC and differential, peripheral blood smear, uric acid, LDH, extended electrolytes, renal function, and blood culture
- specialized tests: BM ± lymph node biopsy, flow cytometry, cytogenetics, molecular studies
- hyperleukocytosis (total WBC >100 x 10^9/L) is a medical emergency
  - presents clinically with respiratory or neurological distress caused by hyperviscosity of blood and leukostasis
  - risk of ICH, pulmonary leukostasis syndrome, tumour lysis syndrome
  - management: fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes), or leukapheresis in some centres

Management
- combination chemotherapy using non-cross resistant chemotherapy agents; allogeneic stem cell transplantation for particular genetic subtypes, poorly refractory disease, or recurrent disease
- supportive care and management of treatment complications
  - febrile neutropenia: see Infectious Diseases, ID44
  - tumour lysis syndrome: see Hematology, H46

Back pain in children must always be investigated!
Unlike adults, back pain in children often points to a pathological process

Prognosis
- 80-90% 5-yr event-free survival for ALL, 65% 5-yr survival for AML
- patients are stratified into standard risk and high-risk based on WBC and age; other prognostic factors include presence of CNS/testicular disease, immunophenotype, cytogenetics, and initial response to therapy (most important prognostic variable)

Lymphoma

- see Hematology, H46

Epidemiology
- Hodgkin lymphoma: incidence is bimodal, peaks at ages 15-34 and >50 yr
- non-Hodgkin lymphoma: incidence peaks at 7-11 yr

Constitutional symptoms = fever, chills, night sweats, unexplained weight loss (≥10% body weight over 6m)

Clinical Features
- Hodgkin lymphoma
  - most common presentation is persistent, painless, firm, rubbery, cervical or supraclavicular lymphadenopathy
  - can present as persistent cough or dyspnea (secondary to mediastinal mass) or less commonly as splenomegaly, axillary, or inguinal lymphadenopathy
  - constitutional symptoms in 30% of children
  - contiguous spread

- non-Hodgkin lymphoma
  - presents as enlarging, non-tender lymphadenopathy
  - includes most commonly mature B cell lymphoma (Burkitt, diffuse large B cell), T cell lymphoblastic, and mature T cell lymphoma (anaplastic large cell)
  - rapidly growing tumour with distant metastases (unlike adult non-Hodgkin lymphoma)
  - signs and symptoms related to disease site: most commonly abdomen (intussusception), chest (mediastinal mass), head and neck region
- investigations: CBC and differential, peripheral blood smear, extended electrolytes, uric acid, LDH, renal function, liver enzymes and function, ESR, and blood culture if concerns for infection. CXR (AP and lateral) and CT of neck/chest/abdomen/pelvis. Specialized tests: BM aspirate and biopsy ± LN biopsy, LP, PET scan

Management
- Hodgkin lymphoma
  - combination chemotherapy and radiation
  - increasing role for use of PET scanning to assess early disease response and plan therapy
- non-Hodgkin lymphoma
  - combination chemotherapy
  - no added benefit of radiation in pediatric protocols

Prognosis
- Hodgkin lymphoma: >90% 5 yr survival
- non-Hodgkin lymphoma: 75-90% 5 yr survival

Brain Tumours

- see Neurosurgery, NS12

Wilms' Tumour (Nephroblastoma)

Epidemiology
- usually diagnosed between 2-5 yr; M=F
- most common primary renal neoplasm of childhood
- 5-10% of cases both kidneys are affected (simultaneously or in sequence)

Differential Diagnosis
- hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma

Clinical Features
- 80% present with asymptomatic, unilateral abdominal mass
- may also present with HTN, gross hematuria, abdominal pain, vomiting, fever, UTI, anemia
- may have pulmonary metastases at time of diagnosis (respiratory symptoms)

Associated Congenital Abnormalities
- WAGR syndrome (Wilms' tumour, Aniridia, Genitourinary anomalies, mental Retardation) with 11p13 deletion
- Beckwith-Wiedemann syndrome:
  - characterized by enlargement of body organs (especially tongue), hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
  - also at increased risk for developing hepatoblastoma, and less commonly adrenocortical tumours, neuroblastomas, and rhabdomyosarcomas
- Denys-Drash syndrome: characterized by gonadal dysgenesis and nephropathy leading to renal failure

Management
- staging ± nephrectomy
- chemotherapy, radiation for higher stages

Prognosis
- >95% 5-yr survival
- prognostic factors include tumour histology and size, molecular and genetic markers, age

Investigations
- CBC, electrolytes, Cr, BUN, urinalysis, coagulation studies
- imaging: U/S, contrast-enhanced CT or MRI chest/abdomen/pelvis

Neuroblastoma

Epidemiology
- most common cancer occurring in first yr of life; average age at diagnosis is 2.5yr
- neural crest cell tumour arising from sympathetic tissues (neuroblasts)

Clinical Features
- can originate from any site in sympathetic nervous system, presenting as mass in neck, chest, or abdomen (most common site is adrenal gland)
- signs and symptoms of disease vary with location of tumour
  - thoracic: dyspnea, Horner's syndrome
  - abdomen: palpable mass, pain, constipation, enuresis
  - paravertebral: spinal cord compression, localized back pain, weakness
- metastases are common at presentation (>50% present with advanced stage disease):
  - usually to bone or bone marrow (presents as bone pain, limp)
  - can also present with periorbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, "blueberry muffin" skin nodules
- paraneoplastic: HTN, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from vasoactive intestinal peptide secretion), opsomyoclonus

Management
- depends on prognostic factors and may include combination of: surgery, radiation, chemotherapy, autologous stem cell transplantation, immunotherapy

Prognosis
- prognosis is often poor due to late detection
- good prognostic factors
  - "age and stage" are important determinants of better outcome: <18 mo, stage I, II, IV-S disease ("S" designates a "Special" classification only pertaining to infants)
  - primary site: posterior mediastinum and neck
  - more differentiated histology
  - tumour cell markers: aneuploidy, absent MYCN oncogene amplification

Investigations
- CBC, electrolytes, urinalysis, urine, catecholamine metabolites (HVA and VMA), Cr
- imaging: MRI or CT, MIBG scan
- biopsy: required for definitive diagnosis and classification
- definitive diagnosis needs one of the following:
  - unequivocal histologic diagnosis from tumour tissue
  - evidence of bone marrow metastases on aspirate biopsy with elevation of urinary/serum catecholamines or metabolites

Bone Tumours

- see Orthopedic Surgery, OR50

Cancer Predisposition Syndromes

- suspected in cases of multiple primary neoplasms, especially early onset for cancer type and/or family history consistent with known cancer predisposition syndrome (critical to obtain family history and refer if syndrome suspected)
- cancer predisposition syndromes with pediatric onset include Li-Fraumeni syndrome (soft tissue sarcomas, osteosarcoma, CNS tumours, and adrenal cortical carcinoma), hereditary retinoblastoma, and Fanconi anemia (leukemias and oral cancers)
- early recognition of new malignancies through surveillance limits required therapies

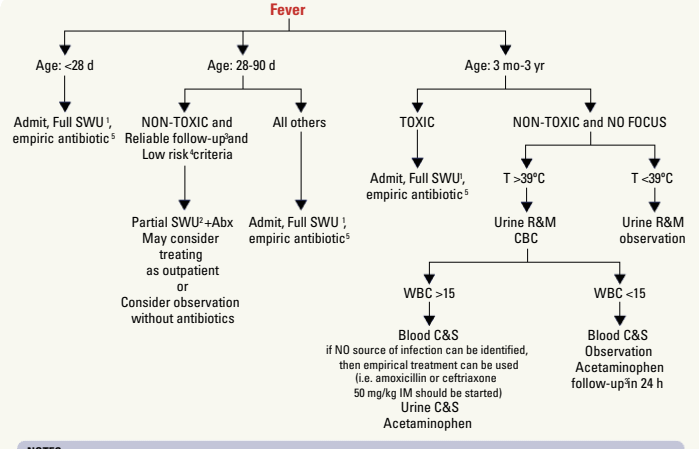
Infectious Diseases

Fever

Definition
- fever: a practical definition is >38°C/100.4°F oral or rectal
- fever without a source/focus: acute febrile illness (typically <10 d duration) with no identifiable cause of fever even after careful history and physical
- fever of unknown origin: daily or intermittent fevers for at least 2 consecutive wk of uncertain cause after careful history and physical, and initial laboratory assessment

Etiology
- infectious: anatomic approach (CNS, ears, upper and lower respiratory tract, GI, GU, skin, soft tissue, bones and joints, etc.)
- inflammatory: mainly autoimmune (Kawasaki disease, JIA, IBD, SLE, etc.)
- malignancy: childhood cancers (leukemia, lymphoma, neuroblastoma, etc.)
- miscellaneous: drugs and toxins, post-immunization, familial dysautonomia, factitious disorder, etc.

Diagnosis
- history: duration, height and pattern of fever, associated symptoms, exposures, constitutional symptoms, recent antipyretic use, ethnic or genetic background, daycare, sick contacts, travel, tick or other bug bites, age of child
- physical exam: toxic vs. non-toxic, vitals, growth, complete head-to-toe exam to identify any focus of infection
- investigations: guided by history, physical exam, and clinical suspicion



NOTES
1. SWU = Septic Workup
2. Partial SWU – blood C&S, CBC and differential, urine R&M, C&S, LP, CXR if respiratory symptoms, stool C&S if GI symptoms
3. Follow-up is crucial – if adequate follow-up is not assured, a more aggressive diagnostic and therapeutic approach may be indicated
4. Low-risk (Rochester) criteria
5. Considerable practice variation exists in terms of empiric antibiotic treatment
6. Important principles – the younger the child, the greater the difficulty to clinically assess the degree of illness

Figure 12. Approach to the febrile child

Rochester Criteria – Developed to Identify Infants ≤60 d of Age with Fever at Low-risk of Serious Bacterial Infection

Clinically	Well
WBC Count	5-15 x 109/L
Bands	<1.5 x 109/L
Urinalysis	<10 WBC/high-power field
Stool (if diarrhea)	<5 WBC/high-power field
Past Health	Born >37 wk Home with/before mom No hospitalizations No prior antibiotic use No prior treatment for unexplained hyperbilirubinemia No chronic disease

Evaluation of Neonates and Infants with Fever
- several protocols exist that attempt to identify neonates and young infants at low-risk of serious bacterial infection (e.g. Rochester Criteria)
  - such protocols are not as sensitive in the 1-28 d age group; therefore, febrile neonates should be considered high-risk regardless of clinical features and laboratory findings

Management
- admit to hospital if appropriate
- treat the source if known
- replace fluid losses (e.g. from vomiting, diarrhea); maintenance fluid needs are higher in a febrile child
- reassure parents that most fevers are benign and self-limited
- antipyretics (acetaminophen and/or ibuprofen) may be given if child is uncomfortable

Acute Otitis Media

- all of:
  1. middle ear effusion
  2. middle ear inflammation
  3. acute onset of symptoms of middle ear effusion and inflammation

Epidemiology
- 60-70% of children have at least 1 episode of AOM before age 3
- 6-24 mo is the most common age group
  - commonly develops within a wk after a viral URI
- one third of children have had ≥3 episodes by age 3; peak incidence January to April

Etiology
- bacterial – S. pneumoniae (decreasing since the introduction of PCV7 and PCV13), H. influenza, M. catarrhalis, group A Streptococcus (GAS)
- less common - anaerobes (newborns) , Gram-negative enterics (infants)
- viral – more likely to spontaneously resolve; RSV, coronaviruses, influenza viruses

Risk Factors
- Eustachian tube related:
  - dysfunction/obstruction (URTI, allergic rhinitis, chronic rhinosinusitis, adenoid hypertrophy, barotrauma)
  - inadequate tensor veli palatini function (cleft palate)
  - genetic syndromes (DS, Crouzon, Apert)
  - cilia disruption (Kartagenger's syndrome, CF)
- genetic predisposition (family history, ethnicity – First Nations peoples and Inuit, low levels of secretory IgA, or persistent biofilm in middle ear)
- behavioural and environmental exposures (not breastfed or shorter duration of breastfeeding, prolonged bottle feeding, bottle feeding laying down, pacifier use, second-hand smoke exposure, crowded living conditions/daycare, sick contacts)
- immunosuppression/deficiency (chemotherapy, steroids, DM, hypogammaglobulinemia, CF)

Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features
- acute onset of symptoms
- triad of otalgia (best predictor of AOM), fever (especially in younger children), and conductive hearing loss – not all symptoms such as fever or hearing loss may be present
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers: ear-tugging (this alone is not a good indicator of pathology), hearing loss, balance disturbances (rare), irritable, poor sleeping, vomiting and diarrhea, anorexia
- otoscopy of TM: hyperemia, bulging, pus may be seen behind TM, loss of landmarks (e.g. handle and long process of malleus not visible), discolouration (hemorrhagic, grey, red, yellow)

Diagnosis
- requires middle ear effusion and signs of inflammation (most important is a bulging TM)
- accurate diagnosis of AOM is very important to prevent antibiotic overuse

Pneumococcal Conjugate Vaccines for Preventing Acute Otitis Media in Children
Cochrane DB Syst Rev 2019:CD001480
Purpose: To systematically review the use of pneumococcal conjugate vaccines in preventing AOM in children <13 years of age.
Methods: RCTs comparing the use of pneumococcal conjugate vaccines to placebo or control vaccine were included in this review.
Results: 14 studies based on 11 trials with a total of 60733 children were included in this review. During early infancy administration of licenced CRM197-PCV7 and PHiD-CV10 vaccines is associated with a large relative reduction in pneumococcal AOM. No beneficial effect was seen for all cause AOM in high-risk infants, after early infancy, or in older children with a history of respiratory illness. Mild adverse reactions (local redness or swelling, fever, pain, tenderness) were seen more commonly in the group receiving the pneumococcal conjugate vaccines compared to placebo or control vaccines. No differences in severe adverse effects were seen.

Management of Acute Otitis Media in Children Six Months of Age and Older
J Pediatr Child Health 2016;21(1):39-44
Recommendations
- Milder disease is usually due to viruses or low virulence bacteria
  - Resolves equally quickly with or without antibiotics
- Bulging tympanic membrane (especially if yellow or hemorrhagic) has a high sensitivity for AOM and is a major diagnostic criterion
  - Likely bacterial
- Perforation of the tympanic membrane with purulent discharge indicates bacterial AOM
- Indications for immediate antibiotic treatment:
  - Highly febrile (≥39°C)
  - Moderately to severely systemically ill
  - Very severe otalgia
  - Significant illness for 48 h
- Antibiotic therapy regime:
  - Amoxicillin remains the clear drug of choice
  - 10-d course for children <2 yr
  - 5-d course for children ≥2 yr
- For milder presentations, plan a reassessment at 48 h OR provide an antibiotic prescription to parents to fill if the child does not improve in 48 h

Management

- symptomatic therapy: antipyretics/analgesics (e.g. acetaminophen or ibuprofen)
- watchful waiting if criteria met
- antibiotic therapy if <6 mo or moderate-severe illness:
  - 1st line: high dose amoxicillin 75-90 mg/kg/d dosed BID x 5 d (10 d if age <2 yr, perforated TM, or recurrent AOM) (if penicillin allergic: cefuroxime-axetil, ceftriaxone)
  - 2nd line: amoxicillin-clavulanic acid, cephalosporins: cefuroxime axetil, ceftriaxone, cefaclor, cefixime
    - used when AOM unresponsive and clinical signs/symptoms persist beyond 48 h of antibiotic treatment, or for treatment of otitis-conjunctivitis syndrome
- signs of a perforated TM should always be treated with antimicrobial therapy (most commonly topical Ciprodex) and examined for complications
- prevention: parent education about risk factors, pneumococcal and influenza vaccines, surgery (e.g. tympanostomy tubes)
  - choice of surgical therapy for recurrent AOM depends on whether local factors (Eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinusitis) are responsible

Complications

- extracranial: hearing loss and speech delay (secondary to persistent middle ear effusion (MEE), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
- intracranial: meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis

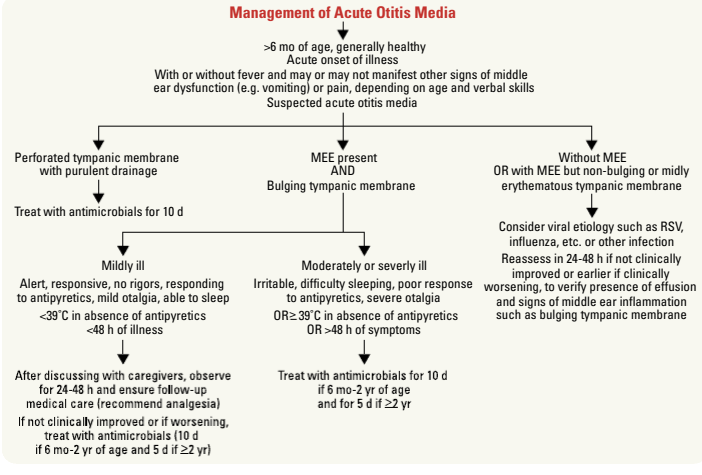

Management of Acute Otitis Media
>6 mo of age, generally healthy
Acute onset of illness
With or without fever and may or may not manifest other signs of middle ear dysfunction (e.g. vomiting) or pain, depending on age and verbal skills
Suspected acute otitis media
Perforated tympanic membrane with purulent drainage
Treat with antimicrobials for 10 d
MEE present AND
Bulging tympanic membrane
Without MEE
OR with MEE but non-bulging or midly erythematous tympanic membrane
Consider viral etiology such as RSV, influenza, etc. or other infection
Reassess in 24-48 h if not clinically improved or earlier if clinically worsening, to verify presence of effusion and signs of middle ear inflammation such as bulging tympanic membrane
Mildly ill
Alert, responsive, no rigors, responding to antipyretics, mild otalgia, able to sleep
<39°C in absence of antipyretics
<48 h of illness
After discussing with caregivers, observe for 24-48 h and ensure follow-up medical care (recommend analgesia)
If not clinically improved or if worsening, treat with antimicrobials (10 d if 6 mo-2 yr of age and 5 d if ≥2 yr)
Moderately or severly ill
Irritable, difficulty sleeping, poor response to antipyretics, severe otalgia
OR≥ 39°C in absence of antipyretics
OR >48 h of symptoms
Treat with antimicrobials for 10 d if 6 mo-2 yr of age and for 5 d if ≥2 yr

Figure 13. Management of acute otitis media
Flow diagram for the management of children with suspected and confirmed acute otitis media – from CPS statement Feb 2016

Otitis Media with Effusion

Definition
- presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology
- most common cause of conductive hearing loss in children
- 90% of cases resolved by 3 mo
- 80-90% of all children have one episode before 6 yr
- 30-40% of affected children will experience recurrent episodes

Risk Factors
- same as AOM

Clinical Features
- fluctuating conductive hearing loss ± tinnitus
- fullness in ear, balance problems
- ± pain, low grade fever
- otoscopy of TM
  - discolouration – amber or dull grey
  - meniscus fluid level behind TM
  - air bubbles
  - retraction pockets/TM atelectasis
  - flat tympanogram
  - most reliable finding with pneumatic otoscopy is immobility

Management
- expectant management appropriate if low risk for speech/language/learning difficulties
- ENT referral if unilateral OME >6 mo, bilateral OME >3 mo with hearing loss, or structural tympanic membrane damage
- consider early ENT referral for children with craniofacial abnormalities or immunodeficiency
- surgical options include myringotomy with tympanostomy (ventilation) tubes ± adenoidectomy (if tonsils enlarged or on insertion of second set of tubes after first set falls out)
- no role for antibiotics, glucocorticoids, antihistamines, or decongestants

Complications
- hearing loss, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma especially when retraction pockets involve pars flaccida
- retraction of tympanic membrane, atelectasis, ossicular fixation

Gastroenteritis

- see Gastroenterology, G5

HIV Infection

- see Infectious Diseases, ID27

Infectious Pediatric Exanthems

Table 29. Common Infectious Pediatric Exanthems

Disease	Pathogen(s)	Incubation Period	Communicability	Mode of Transmission	Rash	Associated Features	Management	Outcomes and Complications
Erythema Infectiosum (i.e. Fifth Disease/ Slapped Cheek)	Parvovirus B19	4-14 d	Low-risk of transmission once symptomatic	Respiratory secretions or infected blood	Appearance: uniform, erythematous, maculopapular 'lacy' rash Timing: 10-17 d after symptoms (immune response) Distribution: bilateral cheeks ('slapped cheeks') with circumoral sparing; may affect trunk and extremities	Initial 7-10 d of flu-like illness and fever Rash may be warm, non-tender, and pruritic Less common presentations include 'gloves and socks syndrome' or STAR complex (sore throat, arthritis, rash)	Supportive	Rash fades over d to wk, but may reappear mo later with sunlight, exercise Transient Aplastic crisis (especially if chronic hemolytic anemia)
Gianotti-Crosti Syndrome (i.e. Papular Acrodermatitis)	EBV and Hepatitis B virus (majority)	Variable	None	None	Asymptomatic or pruritic Appearance: symmetric papules Distribution: face, cheeks, extensor surfaces of the extremities, spares trunk	Viral prodrome May have lymphadenopathy and/or hepatosplenomegaly	Supportive Pain control	Resolves in 3-12 wk
Hand, Foot, and Mouth Disease	Coxsackie group A	3-5 d	Likely 1-7 d after symptoms but may be up to months	Direct and indirect contact with infected bodily fluids, fecal-oral	Appearance: vesicles and pustules on an erythematous base Distribution: mouth, buttocks, acral, but may extend up the extremity	Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue)	Supportive	Resolves in 1 wk Mainly dehydration
Herpes Simplex	HSV 1, 2	1-26 d		Direct contact, often through saliva, vertical transmission at birth, or sexual contact	Grouped vesicles on an erythematous base	Enanthem: vesicles/ erosions in the ANTERIOR oral cavity (buccal mucosa, tongue) May present with herpetic whitlow (autoinoculation)	Mainly supportive Consider oral or topical antivirals	Local: secondary skin infections, keratitis, gingivostomatitis CNS: encephalitis Disseminated hepatitis, DIC Eczema herpeticum
Kawasaki Disease	See *P99*							
Measles	Morbillivirus	8-13 d	4 d before and after rash	Airborne	Appearance: erythematous maculopapular Timing: 3 d after start of symptoms Distribution: starts at hairline and spreads downwards with sparing of palms and soles	Prodrome of cough, coryza, conjunctivitis (3 Cs) Enanthem: Koplik's spots 1-2 d before rash Desquamation Positive serology for measles IgM	Infected: supportive, some evidence for vitamin A. Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure Respiratory isolation, report to Public Health Prevention: MMR vaccine	Secondary bacterial infections: AOM, sinusitis, pneumonia Encephalitis Rare: myocarditis, pericarditis, thrombocytopenia, Stevens-Johnson syndrome, GN, subacute sclerosing panencephalitis
Non-Specific Enteroviral Exanthems	Enteroviruses	Variable	Variable	Direct and indirect contact with infected bodily fluids	Polymorphous rash (macules, papules, vesicles, petechiae, urticaria)	Systemic involvement is rare, but possible	Supportive Diagnosis confirmed using viral cultures (nasopharyngeal and rectal swabs)	Self-limiting
Roseola	Human herpes virus (HHV) 6	5-15 d	Droplet transmission	Saliva Perinatal: transplacental infection, germline cell integration	Appearance: blanching, pink, maculopapular Timing: appears once fever subsides Distribution: starts at the neck and trunk and spreads to the face and extremities	High grade fever 3-5 d Common: irritability, anorexia, lymphadenopathy, erythematous TM and pharynx, Nagayama spots (erythematous papules on soft palate and uvula) Less common: cough, coryza, bulging fontanelles	Supportive	Self-limiting CNS: febrile seizures (10-25%), aseptic meningitis Thrombocytopenia

Table 29. Common Infectious Pediatric Exanthems

Disease	Pathogen(s)	Incubation Period	Communicability	Mode of Transmission	Rash	Associated Features	Management	Outcomes and Complications
Rubella	Rubivirus	14-21 d	7 d before and after eruptions	Droplet	Appearance: pink, maculopapular Timing: 1-5 d after start of symptoms Distribution: starts on face and spreads to neck and trunk	Prodrome of low grade fever and occipital/retroauricular nodes STAR complex (sore throat, arthritis, rash) Positive serology for rubella IgM. Caution to pregnant women with exposure	Supportive Report to Public Health Prevention: MMR vaccine	Excellent prognosis with acquired disease Arthritis may last days to weeks Encephalitis Irreversible defects in congenitally infected patients (i.e. congenital rubella syndrome)
Scarlet Fever	See *P65*							
Varicella	Varicella zoster virus	10-21 d	1-2 d pre-eruptions and 5 d post-eruption	Direct contact, inhalation of lesion aerosols, aerosolized respiratory secretions	Appearance: groups of skin lesions, polymorphic, from macules to papules to vesicles to crusts Timing: 1-3 d after start of symptoms Distribution: generalized	Significant pruritus Malaise, fever Enanthem: vesicular lesions which may become pustular or ulcerate. Caution to pregnant women	Supportive Avoid salicylates (due to risk of Reye syndrome) Consider antivirals Respiratory and contact isolation, report to Public Health Prevention: varicella vaccine	Skin: bacterial suprainfection, necrotizing fasciitis CNS: acute encephalitis and cerebellar ataxia Systemic: hepatitis, DIC Congenital varicella syndrome if intrapartum infection

Infectious Mononucleosis

Definition
- systemic viral infection caused by EBV with multivisceral involvement; often called "the great imitator"

Epidemiology
- peak incidence between 15-19 yr
- ~50% of children in developed countries have a primary EBV infection by 5 yr, but <10% of children develop clinical infection

Etiology
- EBV: a member of herpesviridae
- transmission is mainly through infected saliva ("kissing disease") and sexual activity (less commonly); incubation period of 1-2 mo

Risk Factors
- infectious contacts, sexually active, multiple sexual partners

History
- prodrome: 2-3 d of malaise, anorexia
- infants and young children: often asymptomatic or mild disease
- older children and adolescents: malaise, fatigue, fever, sore throat, abdominal pain (often LUQ), headache, myalgia

Physical Exam
- classic triad: febrile, generalized non-tender lymphadenopathy, pharyngitis/tonsillitis (exudative)
- ± hepatosplenomegaly
- ± periorbital edema, ± rash (urticarial, maculopapular, or petechial) – more common after inappropriate treatment with β-lactam antibiotics
- any "-itis" (including arthritis, hepatitis, nephritis, myocarditis, meningitis, encephalitis, etc.)

Investigations
- heterophile antibody test (Monospot® test)
  - 85% sensitive in adults and older children, but only 50% sensitive if age <4 yr
  - false positive results with HIV, SLE, lymphoma, rubella, parvovirus
- EBV titres (if negative heterophile test or clinical suspicion remains high)
- CBC and differential, blood smear: reactive lymphocytes, lymphocytosis, Downey cells ± anemia ± thrombocytopenia
- throat culture to rule out streptococcal pharyngitis

Management
- supportive: adequate rest, hydration, saline gargles, and analgesics for sore throat
- splenic enlargement is often not clinically apparent so all patients should avoid contact sports for 6-8 wk
- if airway obstruction secondary to nodal and/or tonsillar enlargement is present (especially younger children), admit for steroid therapy

Prognosis
- most acute symptoms resolve in 1-2 wk, though fatigue may last for mo
- short-term complications: splenic rupture, Guillain-Barré syndrome
- infectious pharyngitis/tonsillitis

Definition

- inflammation of the pharynx, especially the tonsils if present, causing a sore throat

Etiology
- viral (~80%): adenoviruses, enteroviruses, coxsackie, upper respiratory tract viruses, EBV, CMV, COVID-19
- bacterial (~20%): mainly GAS, *M. pneumoniae* (older children), *N. gonorrhoeae* (sexually active), *C. diphtheriae* (unvaccinated), *F. necrophorum* (anaerobe causing Lemierre syndrome)
- fungal: Candida

Epidemiology
- season: GAS pharyngitis more common in late winter or early spring; viral all year long
- age: GAS pharyngitis peak incidence at 5-12 yr and uncommon <3 yr; viral pharyngitis affects all ages

Presentation
- GAS: sore throat (may be severe), febrile, malaise, headache, abdominal pain, N/V, absence of other URTI symptoms, pharyngeal/tonsillar erythema and exudates, enlarged (>1 cm) and tender anterior cervical lymph nodes, palatal petechiae, strawberry tongue, scarlatiniform rash
- viral: sore throat (often mild), conjunctivitis, cough, rhinorrhea, hoarseness, diarrhea, flu-like symptoms (fever, malaise, myalgias), absent/mild tonsillar exudates, minor and non-tender adenopathy, viral exanthems

Investigations
- m-CENTOR scores are used to predict if throat culture will be positive
  - these score systems have not been found to be sensitive or specific enough to diagnose GAS in children and adolescents with sore throat
- suspected diagnosis of GAS pharyngitis should be confirmed with a rapid streptococcal antigen test and a follow-up throat culture if the rapid test is negative

Management
- antibiotics (for GAS/*S. pyogenes*)
  - penicillin V or amoxicillin or erythromycin (if penicillin allergy) x 10 d
  - can prevent rheumatic fever if given within 9 d of symptoms; does NOT alter risk of post-streptococcal GN
- supportive: hydration and acetaminophen for discomfort due to pain and/or fever
- follow-up: if uncomplicated course, no follow-up or post-antibiotic throat cultures needed
- prophylaxis: tonsillectomy may be considered for severe, recurrent streptococcal tonsillitis

Complications
- preventable with antibiotics: AOM, sinusitis, cervical adenitis, mastoiditis, retropharyngeal/peritonsillar abscess, sepsis
- immune-mediated complications: scarlet fever, acute rheumatic fever, post-streptococcal GN, reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with GAS (PANDAS)

SCARLET FEVER
- diffuse erythematous eruption
- delayed-type hypersensitivity reaction to pyrogenic exotoxin produced by GAS
- requires prior exposure to *S. pyogenes*
- acute onset of fever, sore throat, strawberry tongue
- 24-48 h after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa; Pastia's lines may be accentuated in flexural areas
- within 24 h, sandpaper rash becomes generalized with perioral sparing, non-pruritic, non-painful, blanchable
- rash fades after 3-4 d, may be followed by desquamation
- treatment is penicillin, amoxicillin, or erythromycin x 10 d

RHEUMATIC FEVER
- inflammatory disease due to antibody cross-reactivity following GAS infection
- affects ~1 in 10000 children in developed world; much more prevalent in developing nations; peak incidence at 5-15 yr
- clinical diagnosis based on Jones Criteria (revised)
  - requires 2 major OR 1 major and 2 minor PLUS evidence of preceding strep infection (history of scarlet fever, GAS pharyngitis culture, positive rapid Ag detection test, ASOTs)
    - major: carditis and valvulitis, arthritis, CNS involvement (Sydenham chorea), subcutaneous nodules, erythema marginatum
    - minor: arthralgia, fever, ↑ESR or CRP, prolonged PR interval
- treatment: penicillin or erythromycin for acute course x 10 d, prednisone if severe carditis
- secondary prophylaxis with daily penicillin or erythromycin
- complications
  - acute: myocarditis, conduction system aberrations (sinus tachycardia, atrial fibrillation), valvulitis (acute mitral regurgitation), pericarditis
  - chronic: valvular heart disease (mitral and/or aortic insufficiency/stenosis), infectious endocarditis ± thromboembolic phenomenon
  - onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever

POST-STREPTOCOCCAL GLOMERULONEPHRITIS
- most common in children ages 4-8 yr; M>F
- antigen-antibody mediated complement activation with diffuse, proliferative GN
- occurs 1-3 wk following initial GAS infection (skin or throat)
- clinical features vary from asymptomatic, microscopic and macroscopic hematuria (cola-coloured urine) to all features of nephritic syndrome (see *Nephritic Syndrome, P83*)
- diagnosed upon clinical findings of acute nephritis and recent GAS infection. It can be confirmed with elevated serum antibody titres against streptococcal antigens (ASOT, anti-DNAase B), low serum complement (C3)
- management
  - symptomatic: fluid and sodium restrictions; loop diuretics for HTN and edema
  - in severe cases, may require dialysis if renal function significantly impaired
  - treat with penicillin or erythromycin (if penicillin allergy) if evidence of persistent GAS infection
- 95% of children recover completely within 1-2 wk; 5-10% have persistent hematuria

m-CENTOR Score for Probability of Streptococcal Pharyngitis
For patients presenting with sore throat/pharyngitis and URTI symptoms:
Must be >3 yr
Cough — no cough (+1)
Exudates or Swelling — tonsillar exudates/swelling (+1)
Nodes — anterior cervical adenopathy (+1)
Temperature — history of fever or temperature >38°C (+1)
Only Young — patients <15 y/o (+1)
Rarely Elder — patients >45 y/o (-1)

Interpretation

m-CENTOR Score	Probability of strep pharyngitis	Recommendation
0	1-2.5%	No further testing or antibiotics
1	5-10%	
2	11-17%	Consider rapid strep testing and/or culture
3	28-35%	
≥4	51-53%	Consider rapid strep testing and/or culture. Empiric antibiotics may be appropriate depending on scenario

Meningitis

Definition
- inflammation of the meninges surrounding the brain and spinal cord

Epidemiology
- peak age: <1 yr; 90% of pediatric cases occur in children age <5 yr

Etiology
- viral: enteroviruses, human parechoviruses, HSV
- bacterial: age-related variation in specific pathogens
- fungal and parasitic meningitis also possible
- most often due to hematogenous spread or direct extension from a contiguous site

Risk Factors
- unvaccinated
- immunocompromised: asplenia, DM, HIV, prematurity
- recent or current infections: AOM, sinusitis, orbital cellulitis
- neuroanatomical: congenital defects, dermal sinus, neurosurgery, cochlear implants, recent head trauma
- exposures: daycare centres, household contact, recent travel

History
- signs and symptoms variable and dependent on age, duration of illness, and host response to infection
- infants: fever, lethargy, irritability, poor feeding, vomiting, diarrhea, respiratory distress, seizures
- children: fever, headache, photophobia, N/V, confusion, back/neck pain/stiffness, lethargy, irritability

Physical Exam
- infants: toxic, hypothermia, bulging anterior fontanelle, respiratory distress, apnea, petechial/purpuric rash, jaundice
- children: toxic, decreased LOC, nuchal rigidity, Kernig's and Brudzinski's signs, focal neurologic findings, petechial/purpuric rash

Investigations

- blood work: CBC, electrolytes, Cr, BUN, glucose, C&S, PTT/INR
- LP required for definitive diagnosis
  - Gram stain, bacterial C&S, WBC count and differential, RBC count, glucose, protein concentration
  - acid-fast stain if suspect TB
  - PCR for specific bacteria if available (helpful if already treated with antibiotics)
  - urinalysis and urine C&S in infants, Gram stain and culture of petechial/purpuric lesions
  - HSV and enterovirus PCR if suspected
  - contraindications: thrombocytopenia, DIC, signs of raised ICP, unstable patient, known/suspected underlying anatomical abnormalities to the lumbar region
  - decision making around LP should NOT delay empiric antibiotic therapy

Table 30. CSF Findings of Meningitis

Component	Normal Child	Normal Newborn	Bacterial Meningitis	Viral Meningitis	Tuberculosis Meningitis
Lymphocytes (x106/L)	≤5	0-30	Usually <100	10-1000 (can be normal)	50-1000 (can be normal)
Neutrophils (x106/L)	0	0	100-10000 (can be normal)	Usually <100	Usually <100
Glucose (CSF:Blood)	≥0.6 (or ≥2.5 mmol/L)	≥0.6 (or ≥2.0 mmol/L)	<0.4 (can be normal)	Usually normal	<0.3 (can be normal)
Protein (g/L)	<0.4	<1.0	>1.0 (can be normal)	0.4-1.0 (can be normal)	1-5 (Can be normal)

Modified from https://www.rch.org.au/clinicalguide/guideline_index/CSF_Interpretation/

Management

- supportive care
  - preservation of adequate cerebral perfusion by maintaining normal BP and managing ICP
  - close monitoring of fluids, electrolytes, glucose, acid-base disturbances, coagulopathies
- bacterial meningitis
  - if suspected or cannot be excluded, commence empiric antibiotic therapy while awaiting cultures or if LP contraindicated or delayed
  - adjuvant dexamethasone BEFORE antibiotic for Hib meningitis; consider for those >6 wk with pneumococcal meningitis
  - isolation with appropriate infection control procedures until 24 h after culture-sensitive antibiotic therapy
  - fluid restrict if any concern for SIADH
  - hearing test
  - report to Public Health; prophylactic antibiotics for close contacts of Hib and N. meningitidis meningitis
- viral meningitis
  - mainly supportive (except for HSV)
  - acyclovir for HSV meningitis
  - report to Public Health
- prophylaxis: appropriate vaccinations significantly decrease incidence of bacterial meningitis (see *Routine Immunization, P5*)

Table 31. Antibiotic Management of Bacterial Meningitis

Age	Main Pathogens	Antibiotics
0-28 d	GBS, E. coli, Listeria Other: Gram-negative bacilli	Ampicillin + cefotaxime
28-90 d	Overlap of neonatal pathogens and those seen in older children	Cefotaxime + vancomycin (+ ampicillin if immunocompromised)
>90 d	S. pneumoniae, N. meningitidis, H. influenzae	Ceftriaxone ± vancomycin (if penicillin allergic: vancomycin + rifampin)

Signs of Meningismus

BONK on the head
Brudzinski's sign
Opisthotonos*
Nuchal rigidity
Kernig's sign
*Opisthotonos: rigid spasm of the body, with the back fully arched and the heels and head bent back

Complications

- mortality: neonate 15-20%, children 4-8%; pneumococcus > meningococcus > Hib
- acute: SIADH, subdural effusion/empyema, brain abscess, disseminated infection (osteomyelitis, septic arthritis, abscess), shock/DIC
- chronic: hearing loss, neuromotor/cognitive delay, learning disabilities, neurological deficit, seizure disorder, hydrocephalus

Mumps

Definition
- acute, self-limited viral infection most commonly characterized by adenitis and swelling of the parotid glands

Epidemiology
- incidence in Ontario has declined since introduction of two-dose MMR vaccination schedule
- average of 25 reported cases per yr
- majority of reported cases in children age 5-10 yr

Etiology
- mumps virus (RNA virus of the genus Rubulavirus in the Paramyxoviridae family)
- transmission via respiratory droplets, direct contact, fomites
- incubation period: usually 14-16 d (range 12-25 d)
- infectivity period: 7 d pre-parotitis to 5 d post-parotitis
- viral replication in upper respiratory tract, drains to local lymph nodes, then spreads to secondary sites (salivary glands, gonads, pancreas, meninges, kidney, heart, thyroid)

History
- non-specific prodrome of fever, headache, malaise, myalgias (especially neck pain)
- usually followed within 48 h by parotid swelling secondary to parotitis (bilateral, preauricular, ear pushed up and out)
- parotid gland is tender and pain worsened with spicy or sour foods
- one third of infections do not cause clinically apparent salivary gland swelling and may simply present as an URTI

Investigations
- clinical diagnosis, but may be confirmed with IgM positive serology within 4 wk of acute infection
  - may also use PCR or viral cultures from oral secretions, urine, blood, and CSF
  - blood work: CBC (leukopenia with relative lymphocytosis), serum amylase (elevated)

Management
- mainly supportive: analgesics, antipyretics, warm or cold packs to parotid may be soothing
- admit to hospital if serious complications (meningitis, pancreatitis)
- droplet precautions recommended until 5 d after onset of parotid swelling
- prophylaxis: routine vaccination (see *Routine Immunization, P5*)

Complications
- common: aseptic meningitis, orchitis/oophoritis
- less common: encephalitis, pancreatitis, thyroiditis, myocarditis, arthritis, GN, ocular complications, hearing impairment

Pertussis

Definition
- prolonged respiratory illness characterized by paroxysmal coughing and inspiratory "whoop"

Epidemiology
- ~10 million children <1 yr affected worldwide, causes up to 400000 deaths per yr
- greatest incidence among children <1 yr (not fully immunized) and adolescents (waning immunity)

Etiology
- *B. pertussis*: Gram-negative pleomorphic rod
- highly contagious; transmitted via respiratory droplets released during intense coughing
- incubation period: 6-20 d; most contagious during catarrhal phase but may remain contagious for wk after

History
- prodromal catarrhal stage
  - lasts 1-7 d; URTI symptoms (coryza, mild cough, sneezing) with NO or low-grade fever
- paroxysmal stage
  - lasts 4-6 wk; characterized by paroxysms of cough ("100 day cough"), sometimes followed by inspiratory whoop ("whooping cough")
  - infants <6 mo may present with post-tussive apnea, whoop is often absent
  - onset of attacks precipitated by yawning, sneezing, eating, physical exertion
  - ± post-tussive emesis, may become cyanotic before whoop
- convalescent stage
  - lasts 1-2 wk; characterized by occasional paroxysms of cough, but decreased frequency and severity
  - non-infectious, but cough may last up to 6 mo

Investigations
- NP specimen using aspirate or NP swab
  - gold standard: culture using special media (Regan-Lowe agar)
  - PCR to detect pertussis antigens
- blood work: CBC (lymphocytosis) and serology (antibodies against B. pertussis)

Management
- admit if paroxysms of cough are associated with cyanosis and/or apnea and give O_2
- supportive care with attention on nutrition in young infants
- antimicrobial therapy indicated if *B. pertussis* isolated or symptoms present for <21 d
  - use macrolide antibiotics (azithromycin, erythromycin, or clarithromycin)
- droplet isolation until 5 d of treatment and report to Public Health
- prophylaxis
  - macrolide antibiotics for all household contacts
  - prevention with vaccination in infants and children (Pentacel®), and booster in adolescents (Adacel®) (see *Routine Immunization, P5*)

Complications
- pressure-related from paroxysms: subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
- respiratory: sinusitis, pneumonia, aspiration, atelectasis, pneumomediastinum, pneumothorax, alveolar rupture
- neurological: seizures (~3%), encephalopathy, ICH
- mortality: ~0.3%; highest risk in infants <6 mo

Pneumonia

- see Infectious Diseases, ID7 and *Pneumonia, P93*

Periorbital (Preseptal) and Orbital Cellulitis

- see Ophthalmology, OP9

Cardinal Signs of Orbital Cellulitis
Ophthalmoplegia/diplopia
Proptosis
Decreased visual acuity
Pain with extraocular eye movement

Sexually Transmitted Infections

- see Family Medicine, FM46 and Gynecology, GY28

Sinusitis

- see Family Medicine, FM47

Definition
- inflammation of sinuses

Epidemiology
- complication of ≤10% of URTIs in children

Investigations
- clinical diagnosis
- diagnostic imaging is NOT required to confirm diagnosis in children
  - routine CT not recommended, but consider if suspect complications of sinusitis, persistent/recurrent disease, need for surgery

Treatment
- antibiotic therapy (amoxicillin) for all children (although nearly half resolve spontaneously within 4 wk)
- complications: preseptal/orbital (preseptal/orbital cellulitis, orbital abscess, osteomyelitis, etc.), intracranial (meningitis, abscess, etc.), Pott's Puffy tumour (presents with tender soft tissue erythematous swelling of the forehead; symptoms include headache, photophobia, and fever; managed with IV antibiotics and ENT consult)

Urinary Tract Infection

Definition
• infection of the urinary bladder (cystitis) and/or kidneys (pyelonephritis)

Epidemiology
• overall prevalence in infants and young children presenting with fever is 7%
• <4-6 wk: more common in males
• >1 yr: females have 2-4x higher prevalence

Etiology
• majority (>95%) have a single cause (~70% E. coli)
• Gram-negative bacilli: E. coli, Klebsiella, Proteus, Enterobacter, Pseudomonas, Citrobacter
• Gram-positive cocci: S. saprophyticus, Enterococcus

Risk Factors
• non-modifiable: female gender, White, previous UTIs, FMHx
• modifiable: urinary tract abnormalities (VUR, neurogenic bladder, obstructive uropathy, posterior urethral valve), dysfunctional voiding, repeated bladder catheterization, uncircumcised males, labial adhesions, sexually active, constipation, toilet training

History
• infants and young child: often just fever or non-specific symptoms (poor feeding, irritability, FTT, jaundice if <28 d, vomiting)
• older child: fever, urinary symptoms (dysuria, urgency, frequency, incontinence, hematuria), abdominal, and/or flank pain

Physical Exam
• infants and young child: toxic vs. non-toxic, febrile, FTT, jaundice; look for external genitalia abnormalities (phimosis, labial adhesions) and lower back signs of occult myelodysplasia (e.g. hair tufts), which may be associated with neurogenic bladder
• older child: febrile, suprapubic and/or costovertebral angle (CVA) tenderness, abdominal mass (enlarged bladder or kidney); may present with short stature, FTT, or HTN secondary to renal scarring from previously unrecognized or recurrent UTIs

Investigations
• urinalysis, microscopy, C&S
  ▪ sterile specimen: clean catch, catheterization, suprapubic aspiration, or 'Tap and Rub' technique
  ▪ bag specimen can only be used for urinalysis and only to rule out diagnosis
  ▪ urinalysis: leukocyte esterase, nitrites, erythrocytes, hemoglobin
  ▪ microscopy: bacteria, leukocytes, erythrocytes
• diagnosis established if urinalysis suggests infection AND if ≥50000 colony-forming units (CFUs)/mL in catheter specimen OR ≥100000 CFUs/mL in clean catch specimen

Management
• admit if: age <2 mo, urosepsis, persistent vomiting, inability to tolerate oral medication, moderate-severe dehydration, immunocompromised, complex urologic pathology, inadequate follow-up, failure to respond to outpatient therapy
• supportive care: maintenance of hydration and adequate pain control
• antibiotics
  ▪ base on local antimicrobial susceptibility patterns
  ▪ commence broad empiric therapy until results of urine C&S known, and then tailor as appropriate
  ▪ neonates: IV ampicillin and aminoglycoside
  ▪ infants and older children: oral antibiotics (based on local E. coli sensitivity) if outpatient; IV ampicillin and gentamicin if inpatient
  ▪ duration 7-10 d
• imaging
  ▪ renal and bladder U/S for all febrile infants (<2 yr), recurrent febrile UTIs (any age) looking for anatomical abnormalities, hydronephrosis, abscess
  ▪ VCUG not recommended after 1st febrile UTI unless U/S reveals hydronephrosis, obstructive uropathies or other signs suggestive of high-grade VUR
• follow-up:
  ▪ outpatients to return in 24-48 h if no clinical response
  ▪ seek prompt medical evaluation for future febrile illnesses
• prophylaxis: generally not recommended unless higher grades of VUR

Complications
• long-term morbidity: focal renal scarring develops in 8% of patients; long-term significance unknown

Features Suggestive of Pyelonephritis
High-grade fever
Flank or high abdominal pain
CVA tenderness on palpation

Bagged urine specimen not useful for ruling in UTI (high false positive rate >85%), but useful for ruling out UTI (high sensitivity)

Prophylaxis After First Febrile Urinary Tract Infection in Children? A Multicentre, Randomized Controlled, Noninferiority Trial
Pediatrics 2008;122:1064-107
Study: Randomized, controlled, open-label, 2 armed, noninferiority trial.
Patients: 338 patients 2 mo to <7 yr who had a first episode of febrile UTI.
Intervention: No prophylaxis vs. prophylaxis.
Outcome: Recurrence rate of febrile UTI and rate of renal scarring.
Results: No significant difference in recurrence rate or in the rate of renal scarring between the prophylaxis and no prophylaxis group.

Neonatology

Gestational Age and Size

Definitions

- classification by GA
  - preterm: <37 wk (extremely preterm <28 wk, very preterm 28-32 wk, moderate-late preterm 32-37 wk)
  - term: 37-42 wk
  - post-term: >42 wk
- classification by birth weight
  - SGA: 2 SD < mean weight for GA or <10th percentile
  - AGA: within 2 SD of mean weight for GA
  - LGA: 2 SD > mean weight for GA or >90th percentile
- classification of preterm infants by birth weight
  - low birthweight (LBW) <2500 g
  - very low birthweight (VLBW) <1500 g
  - extremely low birthweight (ELBW) <1000 g

Dubowitz/Ballard Scores

GA can be determined after birth using Dubowitz/Ballard scores:

Assessment at delivery of physical maturity (e.g. plantar creases, lanugo, ear maturation) and neuromuscular maturity (e.g. posture, arm recoil) translates into a score from -10 to +50

Higher score means greater maturity (increased GA)

-10=20 wk; +50 =44 wk

Ideal=35-40, which corresponds to GA 38-40 wk

Only accurate ± 2 wk

May be inaccurate in infants who are preterm, postterm, SGA infants

Table 32. Abnormalities of Gestational Age and Size

Features	Causes	Problems
Preterm Infants **<37 wk**	Spontaneous: cause unknown Maternal disease: HTN, DM, cardiac and renal disorders Fetal conditions: multiple pregnancy, congenital abnormalities, macrosomia, RBC isoimmunization, fetal infection Pregnancy issues: placental insufficiency, placenta previa, uterine malformations, previous preterm birth, infection, placental abruption Behavioural and psychological contributors: smoking, alcohol, drug use, psychosocial stressors Sociodemographic factors: advanced age, low socioeconomic status	RDS, apnea of prematurity, neonatal chronic lung disease (bronchopulmonary dysplasia) Feeding difficulties, NEC Hypocalcemia, hypoglycemia, hypothermia Anemia, jaundice Retinopathy of prematurity ICH/IVH PDA
Post-Term Infants **>42 wk**	Most cases unknown Increased in first pregnancies Previous post-term birth Genetic factors	Increased risk of stillbirth or neonatal death Increased birthweight Fetal "postmaturity syndrome": impaired growth due to placental dysfunction Meconium aspiration
SGA Infants **<10th percentile** **Asymmetric (head-sparing): late onset, growth arrest**	Extrinsic causes: placental insufficiency, poor nutrition, HTN, multiple pregnancies, drugs, alcohol, smoking, familial factors, fibroids	Perinatal hypoxia Hypoglycemia, hypocalcemia, hypothermia, hyperviscosity (polycythemia), jaundice,
SGA Infants **Symmetric: early onset, lower growth**	Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic	PDA
LGA Infants **>90th percentile**	Maternal DM Racial or familial factors Increasing parity Previous LGA infant, high BMI, large pregnancy weight gain Certain syndromes	Birth trauma, perinatal depression (meconium aspiration) RDS, TTN Jaundice, polycythemia Hypoglycemia, hypocalcemia

Routine Neonatal Care

- history taking
  - passage of meconium in 24-48 h, urination/number of wet diapers
  - feeding: breast milk or formula, route (breast or bottle), duration, frequency and volume of feeds
  - issues: jaundice, poor feeding, difficulty breathing, cyanosis, seizures
  - weight: discharge weight (close follow-up if >10% below birth weight), initial weight gain (goal 20-25 g/d), number of days until birth weight regained (should regain by day 10-14 of life)
- erythromycin ointment: applied to both eyes for prophylaxis of ophthalmia neonatorum (*N. gonorrhoeae*); no longer recommended by Canadian Pediatric Society but required by law in some provinces/territories
- vitamin K IM: prophylaxis against VKDB
- newborn screening tests in Ontario
  - metabolic disorders (amino acid disorders, organic acid disorders, fatty acid oxidation defects, biotinidase deficiency, galactosemia)
  - blood disorders (sickle cell disease, other hemoglobinopathies)
  - endocrine disorders (CAH, congenital hypothyroidism)
  - others (CF, severe combined immunodeficiency)
  - congenital hearing loss
  - critical congenital heart disease (CCHD)
  - spinal muscular atrophy (SMA)
  - congenital CMV
  - parent screen for billiary atresia
- if mother not tested: send cord blood for blood group and DAT (also consider requesting cord blood DAT if O positive mother)
- if household contact is HBsAg positive: start hepatitis B vaccine series (and if mother is positive, give HBIg within 12 h of birth); the US and some Canadian provinces give Hep B vaccine at birth routinely

Neonatal Resuscitation

- assess Apgar score at 1 and 5 min
- if <7 at 5 min then reassess q5 min, until >7
- do not wait to assign Apgar score before initiating resuscitation

Table 33. Apgar Score

Sign	0	1	2
Heart Rate	Absent	<100/min	>100/min
Respiratory Effort	Absent	Slow, irregular	Good, crying
Irritability	No response	Grimace	Cough/cry
Tone	Limp	Some flexion of extremities	Active motion
Colour	Blue, pale	Body pink, extremities blue (acrocyanosis)	Completely pink

Initial Resuscitation

- anticipation: know maternal history, history of pregnancy, labour, and delivery
- steps to take for all infants
  - pre-delivery team debriefing including assigning roles, checking equipment, and discussing possible complications and management plan
  - warm (radiant heater, warm blankets) and dry the newborn (remove wet blankets)
  - stimulate infant: rub lower back gently or flick soles of feet
  - position airway ("sniffing" position) and clear or suction if necessary
  - assess breathing and HR
  - if apneic or ineffective respiration and HR <100: bag and mask ventilation (PPV) with room air (or 30% if preterm infant). Continue until HR >100 and breathing spontaneously
  - if HR <60: establish airway for effective ventilation and start chest compressions; turn oxygen to 100%
  - if meconium present: a team with advanced resuscitation skills should be present. If the newborn is hypotonic with ineffective respirations, routine intubation for tracheal suction is not suggested unless skilled at intubation. Do initial resuscitation and administer PPV as required

Apgar Score

Appearance (colour)
Pulse (heart rate)
Grimace (irritability)
Activity (tone)
Respiration (respiratory effort)
Or: "How Ready Is This Child?"

Use of 100% Oxygen in Neonatal Resuscitation
Circulation 2015;132(suppl 2):S543-S560
The 2015 neonatal resuscitation guidelines have provided the following recommendation: "Since an oxygen saturation of 100% may correspond to a PaO2 anywhere between ~80 and 500 mmHg, in general it is appropriate to wean the FIO2 for a saturation of 100%, provided the oxyhemoglobin saturation can be maintained ≥94%." (Class IIb, LOE C).

Corrective Actions for PPV in Neonatal Resuscitation

MR SOPA
Mask readjustment
Reposition airway
Suction mouth and nose
Open mouth
Pressure increase
Alternative airway

Table 34. Interventions Used in Neonatal Resuscitation

Intervention	Schedule	Indications	Comments
Epinephrine (adrenaline)	0.1-0.3 mL/kg/dose of 1:10000 (0.01-0.03 mg/kg) IV 0.5-1 mL/kg/dose of 1:10000 (0.05-0.1 mg/kg) endotracheally can be considered while awaiting IV access (IV preferred) Can be repeated q3-5 min PRN	HR <60 and not rising	Side effects: tachycardia, HTN, cardiac arrhythmias
Fluid Bolus (NS, PRBC)	10 mL/kg May need to be repeated Avoid giving too rapidly as large volume rapid infusions can be associated with IVH	Evidence of hypovolemia	

Approach to the Depressed Newborn

- a depressed newborn has ineffective respiratory effort and cyanosis
- approximately 10% of newborn babies require assistance with breathing after delivery

Table 35. Etiology of Respiratory Depression in the Newborn

Etiology	Examples
Respiratory Problems	RDS/hyaline membrane disease Pulmonary hypoplasia CNS depression MAS Pneumonia Pneumothorax Pleural effusions Congenital malformations
Anemia (severe)	Erythroblastosis fetalis Secondary hydrops fetalis
Maternal Causes	Drugs/anesthesia (opiates, magnesium sulphate) DM
Congenital Malformations/Birth Injury	Nuchal cord, perinatal depression Bilateral phrenic nerve injury Potter's sequence
Shock	Antepartum hemorrhage
CHD	Transposition of the great arteries with intact ventricular septum
Other	Hypothermia Hypoglycemia Infection

Diagnosis

- vital signs including pre- and post-ductal oxygen saturations and 4 limb BP, hyperoxia test (second line test)
- detailed maternal and labour history: include prenatal care, illnesses, use of drugs, previous high-risk pregnancies, infections during pregnancy (including GBS status), duration of ruptured membranes, maternal fever or signs of chorioamnionitis during labour/delivery, blood type and Rh status, serologies, amniotic fluid status, GA, meconium, Apgar scores
- clinical findings (observe for signs of respiratory distress such as cyanosis, tachypnea, retractions, grunting, temperature instability, poor tone, abnormal movements, no spontaneous movements)
- laboratory results (CBC, blood gas, blood type and DAT, glucose ± blood culture)
- transillumination of chest to evaluate for pneumothorax if sudden change in respiratory status/ worsening distress
- CXR, ECG, echocardiogram, MRI, cerebral function monitoring/EEG

Management

- identify and treat underlying cause

Common Conditions of Neonates

Apnea

Definition

- periodic breathing: normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with pauses lasting 5-10 s
- apnea: absence of respiratory gas flow for >20 s (or less if associated with bradycardia or desaturation)
- three types of apnea
  - central: no chest wall movement, no signs of obstruction
  - obstructive: chest wall movement continues against obstructed upper airway, no airflow
  - mixed: combination of central and obstructive apnea

Differential Diagnosis
- in term infants, apnea requires full septic workup (CBC and differential, blood and urine cultures ± LP, CXR)
- other causes
  - CNS: seizures, ICH
  - apnea of prematurity (<34 wk): CNS immaturity; resolves by 36 wk GA
  - hypoxic injury
  - infectious: sepsis, meningitis, NEC
  - GI: GERD, aspiration with feeding
  - metabolic: hypoglycemia, hyponatremia, hypocalcemia, inborn error of metabolism
  - cardiovascular: anemia, hypovolemia, PDA, heart failure
  - medications: morphine

Management
- O2, ventilatory support, maintain normal blood gasses
- tactile stimulation
- correct underlying cause
- medications: methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)
- if apnea of prematurity is diagnosed, infants should receive cardiorespiratory monitoring in a neonatal intensive care unit and all babies need an apnea-free period of time prior to discharge

Bleeding Disorders in Neonates

Clinical Features
- oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), subgaleal hemorrhage, and prolonged bleeding following circumcision

Etiology
- 4 major categories
  - increased platelet destruction: maternal ITP or SLE, infection/sepsis, DIC, neonatal alloimmune thrombocytopenia, autoimmune thrombocytopenia
  - decreased platelet production/function: pancytopenia, bone marrow replacement, Fanconi anemia, Trisomy 13 and 18
  - metabolic: congenital thyrotoxicosis, inborn error of metabolism
  - coagulation factor deficiencies (see Hematology, H55): hemophilia A/B, VKDB

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Definition
- maternal antibodies directed towards neonatal platelets, causing thrombocytopenia (platelets <150000/μL)

Epidemiology
- 1 in 4000-5000 live births

Pathophysiology
- platelet equivalent of Rh disease of the newborn
- occurs when mother is negative for HPA and fetus is positive
- development of maternal IgG antibodies against HPA antigens on fetal platelets

Clinical Features
- petechiae, purpura, thrombocytopenia in otherwise healthy neonate
- severe disease can lead to intracranial bleeding

Diagnosis
- maternal and paternal platelet typing and identification of platelet alloantibodies

Treatment
- IVIg to mother prenatally starts in second trimester ± steroids ± fetal platelet transfusions
- platelet transfusion is the mainstay of treatment. HPA specific (e.g. HPA-1a negative) platelets are preferred, however can use random donor platelets. Maternal washed platelets are effective but practically often not feasible.
- concomitant IVIG treatment could be considered (insufficient evidence to support routine use)

AUTOIMMUNE THROMBOCYTOPENIA

Pathophysiology
- caused by antiplatelet antibodies from maternal ITP or SLE
- passive transfer of anti-platelet antibodies across placenta

Clinical Features
- similar presentation to neonatal alloimmune thrombocytopenia, but thrombocytopenia is usually less severe and does not tend to cause bleeding

Treatment
- steroids to mother for 10-14 d prior to delivery or IVIg to mother before delivery
- treat neonate with IVIg if active bleeding, platelets <20,000/μL in the absence of bleeding, or babies who are more precarious (e.g. premature or those who are sick and have platelets <50,000/μL); otherwise close monitoring for platelet recovery, bleeding
- transfusion of infant with maternal/donor platelets only in severe cases, as antibodies will destroy transfused platelets

VITAMIN K DEFICIENCY BLEEDING
- see *Vitamin K Deficiency, P53*

Bronchopulmonary Dysplasia

Definition
- also known as neonatal chronic lung disease
- clinically defined as persistent O_2 dependency up to 28 d of life then further classified based on status of baby at 36 wk corrected GA
  - mild: babies who have been weaned from O_2 by 36 wk
  - moderate: babies who require up to 30% by 36 wk
  - severe: babies who require >30% O_2 or CPAP (or mechanical ventilation) at 36 wk
- damage to developing lungs with prolonged intubation/ventilation, high levels O_2, infections

Investigations
- CXR findings may demonstrate decreased lung volumes, areas of atelectasis, signs of inflammation, and hyperinflation

Treatment
- no clearly effective treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, but use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcomes (there is significant practice variation and evolving evidence regarding the use of diuretics and corticosteroids (systemic and inhaled))

Prognosis
- chronic respiratory failure may lead to pulmonary HTN, poor growth, and right-sided heart failure
- patients with bronchopulmonary dysplasia may continue to have significant impairment and deterioration in lung function late into adolescence
- some lung abnormalities may persist into adulthood including airway obstruction, airway hyper-reactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcomes

Cyanosis

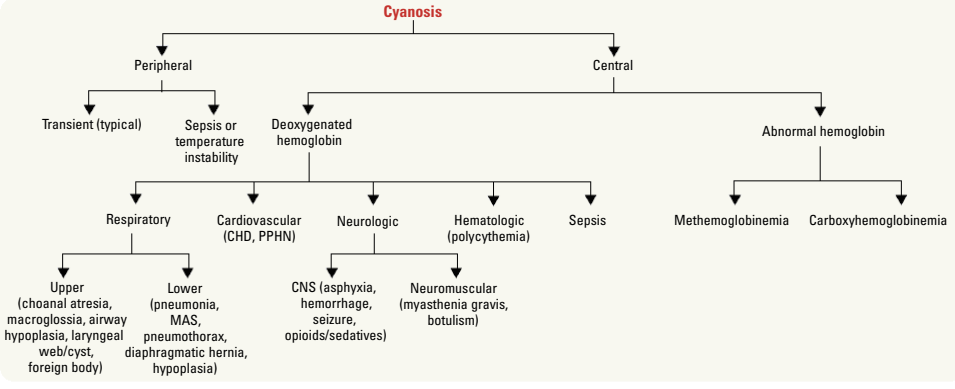


Figure 14. Approach to neonatal cyanosis

Management

- ABGs
  - elevated CO_2 suggests respiratory cause
  - hyperoxia test (to distinguish between cardiac and respiratory causes of cyanosis): get baseline PaO_2 in room air, then PaO_2 on 100% O_2 for 10-15 min
    - PaO_2 <150 mmHg: suggests cyanotic CHD or possible PPHN
    - PaO_2 >150 mmHg: suggests cyanosis likely due to respiratory or non-cardiac cause
  - pulse oximetry is recommended for detection of CHD, although not routinely used
- CXR: look for respiratory abnormalities (pneumothorax, respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)

Diaphragmatic Hernia

- see General and Thoracic Surgery, GS73

Definition

- developmental defect of the diaphragm with herniation of abdominal organs into thorax
- associated with pulmonary hypoplasia and PPHN

Clinical Features

- respiratory distress, cyanosis
- scaphoid abdomen and barrel-shaped chest
- affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
- heart sounds shifted to contralateral side, if left sided diaphragmatic hernia
- asymmetric chest movements, trachea deviated away from affected side
- may present outside of neonatal period
- often associated with other anomalies (cardiovascular, neural tube defects, chromosomal abnormalities)
- CXR for diagnosis: bowel loops in thorax (usually left side), displaced mediastinum

Treatment

- immediate intubation required at birth: DO NOT bag mask ventilate because air will enter stomach and further compress lungs
- place large bore orogastric tube to decompress bowel
- initial stabilization and management of pulmonary hypoplasia and PPHN if present, hemodynamic support and surgery when stable

Hypoglycemia

Definition
- glucose <2.6 mmol/L within 72 h of birth OR <3.3 mmol/L after first 72 h of life

Etiology
- decreased carbohydrate stores: premature, SGA
- endocrine: hormonal deficiencies (GH, cortisol, epinephrine), insulin excess (infant of maternal GDM, LGA, Beckwith-Wiedemann syndrome/islet cell hyperplasia), hypothalamic-pituitary-adrenal axis suppression (panhypopituitarism)
- inborn errors of metabolism: fatty acid oxidation defects, galactosemia
- miscellaneous: sepsis, hypothermia, polycythemia, perinatal stress (e.g. asphyxia), maternal labetolol use (common with preeclampsia)

Clinical Findings
- signs often non-specific and subtle: jitteriness, lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

Management
- identify and monitor infants at risk (pre-feed blood glucose checks) until blood glucose stable and for at least 12 h (for infant of maternal GDM or LGA) or 24 h (if preterm or SGA)
- in a well at-risk infant, begin oral feeds as soon as possible after birth and ensure regular feeds, check glucose at 2 h of age
- if significant and/or symptomatic hypoglycemia, provide glucose IV (D10W) and titrate according to blood sugar levels
- if persistent hypoglycemia (>72 h of life and glucose <2.8 mmol/L), prolonged glucose IV, severe symptomatic hypoglycemia (coma, lethargy, seizure), or no predisposing cause, send "critical blood work" during an episode of hypoglycemia: confirmatory plasma glucose, ABG, ammonia, β-hydroxybutyrate, cortisol, carnitine, acylcarnitine profiling, free fatty acids, GH, insulin, lactate, urine dipstick for ketones

Neonatal Hyperbilirubinemia

Definition
- total serum bilirubin >95th percentile (high-risk zone) on Bhutani nomogram in infants >35 wk GA

Clinical Features
- jaundice typically visible at serum bilirubin levels of 85-120 μmol/L
- visual assessment is misleading, confirm jaundice with blood test

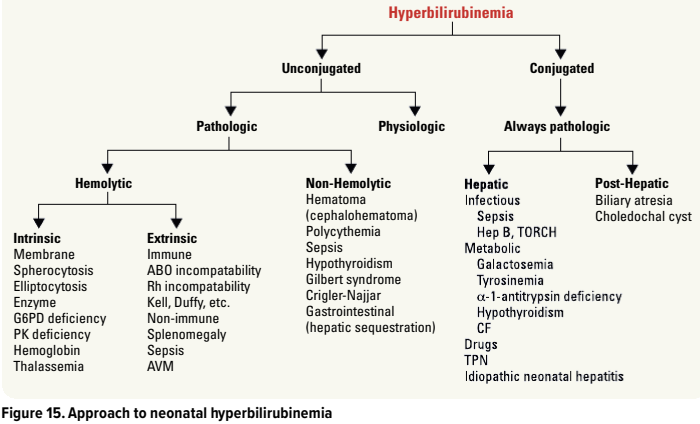


Figure 15. Approach to neonatal hyperbilirubinemia

Jaundice is very common – 60% of term newborns develop visible jaundice

Jaundice in the first 24 h of life and conjugated hyperbilirubinemia are always pathological

Jaundice must be investigated if:

It occurs within 24 h of birth

Conjugated hyperbilirubinemia is present

Unconjugated bilirubin rises rapidly or is excessive for patient's age and weight

Persistent jaundice lasts beyond 1-2 wk of life

PHYSIOLOGIC JAUNDICE

Epidemiology
- term infants: onset 3-4 d of life, resolution by 10 d of life
- premature infants: higher peak and longer duration

Pathophysiology
- increased hematocrit and decreased RBC lifespan
- immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
- increased enterohepatic circulation

Breastfeeding Jaundice
- common: due to baby not getting enough milk (e.g. related to latch, a lack of milk production) → dehydration → exaggerated physiologic jaundice

Breast Milk Jaundice
- 1 in 200 breastfed infants
- glucuronyl transferase inhibitor found in breast milk
- onset 7 d of life, peak at 2-3 wk of life, usually resolved by 6 wk

Table 36. Risk Factors for Jaundice

Maternal Factors	Perinatal Factors	Neonatal Factors
Ethnic group (e.g. Asian, Indigenous)	Birth trauma (cephalohematoma, ecchymoses)	Difficulty establishing breastfeeding
Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility)	Prematurity	Infection (sepsis, hepatitis)
Breastfeeding		Genetic factors
FMHx/previous child required phototherapy		Polycythemia
Age of mother >25 yr		Drugs
		TPN
		Male sex

Table 37. Causes of Neonatal Jaundice by Age

<24 h	24-72 h	72-96 h	Prolonged (>1 wk)
ALWAYS PATHOLOGIC	Physiologic, polycythemia	Physiologic ± breastfeeding	Breast milk jaundice
Hemolytic	Dehydration (breastfeeding jaundice)	Sepsis	Prolonged physiologic jaundice in preterm
Rh or ABO incompatibility	Hemolysis		Hypothyroidism
Sepsis	G6PD deficiency		Neonatal hepatitis
Congenital infection (TORCH)	Pyruvate kinase deficiency		Conjugation dysfunction
Severe bruising/hemorrhage	Spherocytosis		e.g. Gilbert syndrome,
	Bruising, hemorrhage,		Crigler-Najjar syndrome
	hematoma		Inborn errors of metabolism
	Sepsis/congenital infection		e.g. galactosemia
			Biliary tract obstruction
			e.g. biliary atresia

PATHOLOGIC JAUNDICE
- all cases of conjugated hyperbilirubinemia; some cases of unconjugated hyperbilirubinemia are pathologic

Investigations
- unconjugated hyperbilirubinemia
  - hemolytic workup: CBC, reticulocyte count, blood group (mother and infant), peripheral blood smear, Coombs test (DAT)
  - if baby is unwell or has fever: septic workup (CBC and differential, blood and urine cultures ± LP, CXR)
  - other: G6PD screen (especially in males), TSH
- conjugated hyperbilirubinemia must be investigated without delay
  - consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic workup, galactosemia screen (erythrocyte galactose-1-phosphate uridyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat chloride
- predicting occurrence of severe hyperbilirubinemia
  - measure either total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) concentration in all infants between 24 h and 72 h of life and plot on appropriate hyperbilirubinemia treatment graph. If infant does not require immediate treatment, results should be plotted on predictive nomogram to determine the risk of progression to severe hyperbilirubinemia and need for repeat measurement (refer to: http://www.cps.ca/documents/position/hyperbilirubinemia-newborn))

TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA

- to prevent kernicterus
- breastfeeding does not usually need to be discontinued, ensure adequate feeds and hydration
- lactation consultant support, mother to pump after feeds
- treat underlying causes (e.g. sepsis)
- phototherapy (blue-green wavelength, not UV light); standard intensive or multiple intensive protocol depending on severity of hyperbilirubinemia
  - insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
  - serum bilirubin should be monitored during and immediately after therapy (risk of rebound because photoisomerization is reversible when phototherapy is discontinued)
  - contraindicated in conjugated hyperbilirubinemia: results in "bronzed" baby
  - side effects: skin rash, diarrhea, eye damage (eye shield used routinely for prevention), dehydration
  - use published guidelines and nomogram (see *Figure 16*) to determine appropriateness of phototherapy by stratifying infant risk and assessing if total serum bilirubin level is above cutoff for respective gestational age
- exchange transfusion
  - indications: high bilirubin levels as per published graphs based on age, wk gestation
  - most commonly performed for hemolytic disease and severe cases of G6PD deficiency
  - use of IVIg in case of severe hyperbilirubinemia (DAT+) which is at or near exchange level (standard of care)

"Bronzed" Baby in Infants with Conjugated Hyperbilirubinemia Phototherapy results in the production and accumulation of a toxic metabolite which also imparts a bronze hue on the baby's skin

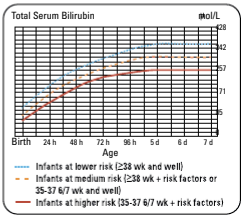


Figure 16. Gold standard in deciding when to initiate phototherapy for unconjugated hyperbilirubinemia
Licence number: 4601410094382

KERNICTERUS

Etiology

- unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin is deposited in the brain resulting in tissue necrosis and permanent damage (typically basal ganglia or brainstem)
- incidence increases as serum bilirubin levels increase above 340 μmol/L
- can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, acidosis, hypothermia, hypoglycemia, and prematurity

Clinical Features

- up to 15% of infants have no obvious neurologic symptoms
- early stage: lethargy, hypotonia, poor feeding, emesis (acute bilirubin encephalopathy)
- mid stage: hypertonia, high pitched cry, opisthotonic posturing (back arching), bulging fontanelle, seizures, pulmonary hemorrhage
- late stage (during first year and beyond): hypotonia, delayed motor skills, extrapyramidal abnormalities (choreoathetoid CP), gaze palsy, mitral regurgitation, sensorineural hearing loss

Prevention

- exchange transfusion, IVIg if indicated

BILIARY ATRESIA

Definition

- atresia of the extrahepatic bile ducts which leads to cholestasis and increased conjugated bilirubin after the first wk of life
- progressive obliterative cholangiopathy

Epidemiology

- incidence: 1 in 10000-15000 live births
- associated anomalies in 10-35% of cases: situs inversus, congenital heart defects, polysplenia

Clinical Features

- dark urine, pale stool, jaundice (persisting for >2 wk), abdominal distension, hepatomegaly

Diagnosis

- conjugated hyperbilirubinemia, abdominal U/S, operative cholangiogram
- HIDA scan (may be bypassed in favour of biopsy if timing of diagnosis is critical)
- liver biopsy

Treatment

- surgical drainage procedure
- hepatoportoenterostomy (Kasai procedure; most successful if age <8 wk)
- two-thirds will eventually require liver transplantation
- vitamins A, D, E, and K; diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

Necrotizing Enterocolitis

Definition
- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon

Epidemiology
- affects 1-5% of preterm newborns admitted to NICU

Pathophysiology
- postulated mechanism of bowel ischemia: mucosal damage and enteral feeding → bacterial growth → bowel necrosis/gangrene/perforation

Risk Factors
- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis
- congenital heart disease and IUGR (anything affecting gut perfusion/reperfusion)

Clinical Features
- usually presents at age 2-3 wk
- distended abdomen, diminished bowel sounds, feeding intolerance
- increased amount of gastric aspirate/vomitus with bile staining
- frank or occult blood in stool
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

Investigations
- AXR: pneumatosis intestinalis (intramural air is a hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, lactate, blood culture, electrolytes
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnia

Treatment
- NPO (7-10 d), vigorous IV fluid resuscitation, decompression with NG tube, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 d)
- serial AXRs detect early perforation (40% mortality in perforated NEC)
- peritoneal drain/surgery if perforation
- surgical resection of necrotic bowel and surgery for complications (e.g. perforation, strictures)

Influence of Enteral Nutrition on Occurrences of Necrotizing Enterocolitis in Very-Low-Birth-Weight Infants
J Pediatr Gastroenterol Nutr 2015;61(4):445-450
Study: Case-control study of very-low-birth-weight (VLBW) infants and occurrences of NEC within 30 d of life.
Population: 1028 VLBW infants in neonatal intensive care unit Jan 2003-May 2008.
Primary Outcome: NEC defined using stage ≥2 of modified Bell criteria.
Results: 55 infants developed NEC within 30 d of life (5.4%). Those with NEC had higher odds of having been fed breast milk <7 d (OR: 4.02), not having achieved full enteral feeding during the first mo (OR: 3.50), and having had parenteral feeding (OR: 2.70).
Conclusions: Occurrence of NEC can be reduced with breast milk feeding beyond 7 d and early full enteral feeding.

Persistent Pulmonary Hypertension of the Newborn

Definition
- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- classified as primary (absence of risk factors) or secondary

Epidemiology
- incidence 1.9 in 1000 live births

Clinical Features
- usually presents within 12 h of birth with severe hypoxemia/cyanosis; some may have only mild respiratory distress

Pathophysiology
- elevated pulmonary pressures cause R → L shunt through PDA, foramen ovale → decreased pulmonary blood flow and hypoxemia → further pulmonary vasoconstriction

Risk Factors
- secondary PPHN: asphyxia, meconium aspiration syndrome, RDS, sepsis, pneumonia, structural abnormalities (e.g. diaphragmatic hernia, pulmonary hypoplasia)
- more common in term or post-term infants

Investigations
- measure pre- and post-ductal oxygen levels
- hyperoxia test to exclude CHD
- pulse oximetry is recommended for detection of CHD, although not routinely used
- echo reveals increased pulmonary arterial pressure and a R → L shunt across PDA and patent foramen ovale; also used to rule out other cardiac defects

Treatment
- maintain good oxygenation (SaO_2 >95%) in at-risk infants
- O_2 given early and tapered slowly, minimize stress and metabolic demands, maintain normal blood gases, circulatory support
- mechanical ventilation, high frequency oscillation in a sedated muscle-relaxed infant
- minimizing handling and use of sedation are hallmarks of treatment
- pressor agents (e.g. milrinone)
- nitric oxide, surfactant
- extracorporeal membrane oxygenation used in some centres when other therapy fails

Respiratory Distress in the Newborn

Clinical Features
- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, subcostal/intercostal indrawing, nasal flaring
- duskiness, central cyanosis
- decreased air entry, crackles on auscultation

Differential Diagnosis of Respiratory Distress
- see Table 33 under *Neonatal Resuscitation, P71*

Investigations
- labs: CBC, blood gas, glucose, blood culture
- imaging: CXR
- if indicated: ECG, echo, LP (CSF cell count, culture, and chemistry)

Table 38. Distinguishing Features of RDS, TTN, MAS

	RDS	TTN	MAS
Etiology	Surfactant deficiency → poor lung compliance due to high alveolar surface tension → atelectasis → ↓ surface area for gas exchange → hypoxia + acidosis → respiratory distress "Hyaline membrane disease"	Delayed resorption of fetal lung fluid → accumulation of fluid in peribronchial lymphatics and vascular spaces → tachypnea "Wet lung syndrome"	Meconium is sterile but causes airway obstruction, chemical inflammation, and surfactant inactivation leading to chemical pneumonitis
Gestational Age	Preterm	Usually term and late preterm	Term and post-term
Risk Factors	Maternal DM Preterm delivery Male sex LBW Acidosis, sepsis Hypothermia Second born twin	Maternal DM Maternal asthma Male sex Macrosomia (>4500 g) Elective Cesarean section or short labour Late preterm delivery	Meconium-stained amniotic fluid Post-term delivery
Clinical Features	Respiratory distress within first few hours of life, worsens over next 24-72 h Hypoxia Cyanosis	Tachypnea within the first few hours of life ± retractions, grunting, nasal flaring Often NO hypoxia or cyanosis	Respiratory distress within hours of birth Small airway obstruction, chemical pneumonitis tachypnea, barrel chest with audible crackles Hypoxia
CXR Findings	Homogenous infiltrates Air bronchograms Decreased lung volumes May resemble pneumonia (GBS) If severe, "white-out" with no differentiation of cardiac border	Perihilar infiltrates "Wet silhouette;" fluid in fissures	Hyperinflation Patchy atelectasis Patchy and coarse infiltrates 10-20% have pneumothorax
Prevention	Prenatal corticosteroids (e.g. Celestone® 12 mg q24 h x 2 doses) if risk of preterm delivery <34 wk Monitor lecithin:sphingomyelin (L/S) ratio with amniocentesis, L/S >2:1 indicates lung maturity	Where possible, avoidance of elective Cesarean delivery, particularly before 38 wk GA	If infant is depressed at birth, intubate and suction below vocal cords (not part of the current NRP sequence, but can be done based on clinical judgement) Avoidance of factors associated with in utero passage of meconium (e.g. post-term delivery)
Treatment	Resuscitation Oxygen Ventilation Surfactant (decreases alveolar surface tension, improves lung compliance, and maintains functional residual capacity)	Supportive Oxygen if hypoxic Ventilator support (e.g. CPAP) IV fluids and NG tube feeds if too tachypneic to feed orally	Resuscitation Oxygen Ventilatory support Surfactant Inhaled nitric oxide Extracorporeal membrane oxygenation for PPHN
Complications	In severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia	Hypoxemia Hypercapnia Acidosis PPHN	Hypoxemia Hypercapnia Acidosis PPHN Pneumothorax Pneumomediastinum Chemical pneumonitis Secondary surfactant inhibition Respiratory failure
Prognosis	Dependent on GA at birth and severity of underlying lung disease; long-term risks of chronic lung disease	Recovery usually expected in 24-72 h	Dependent on severity, mortality up to 20%

PNEUMONIA

- see *Respirology, P68*
- consider in infants with prolonged (≥18 h) or premature rupture of membranes, maternal fever or other signs and symptoms of chorioamnionitis, or if mother is GBS positive
- suspect if infant exhibits respiratory distress, temperature instability, or WBC is low (<5 x 109/L), elevated (>30 x 109/L), or left-shifted
- symptoms may be non-specific (e.g. lethargy, apnea, tachycardia, poor perfusion, poor feeding)
- investigations: CXR (hazy lung and/or distinct infiltrates, may be difficult to differentiate from RDS), chest ultrasound (confirms pleural effusion in complicated pneumonia), blood and CSF cultures
- neonates with pneumonia should be admitted to the NICU and given empiric antibiotics for management

Retinopathy of Prematurity

- see Ophthalmology, OP40

Sepsis in the Neonate

Table 39. Sepsis Considerations in the Neonate

Early Onset (<72 h)	Late Onset (72 h - 28 d)
Vertical transmission, 95% present within 24 h after birth Risk factors: Maternal infection: UTI, GBS positive, previous child with GBS, sepsis, or meningitis Maternal fever/leukocytosis/chorioamnionitis Prolonged rupture of membranes (>18 h) Preterm labour Pathogens: GBS, E. coli, Listeria are most common Pneumonia more common with early-onset sepsis	Acquired after birth Risk factors: preterm infants in NICU Pathogens: coagulase-negative Staphylococcus most common, GBS, anaerobes, E. coli, Klebsiella

Chronic Perinatal Infections

CHEAP TORCHES
Chicken pox/shingles
Hepatitis B/C/D/E
Enteroviruses
AIDS (HIV)
Parvovirus B19 (erythema infectiosum)
Toxoplasmosis
Other
Rubella virus
Cytomegalovirus/Coxsackievirus
HSV
Every STI
Syphilis

Clinical Features

- no reliable absolute indicator of occult bacteremia in infants <3 mo, most specific result has been WBC <5x10⁹/L
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distension, diarrhea
- hypotonia, seizures
- jaundice, hepatomegaly, petechiae, purpura

Investigations

- suspicion of neonatal sepsis requires "full septic workup"
  - CBC, blood cultures, LP (CSF analysis: cell count, glucose, protein, culture, and PCR for viruses) ± CXR
  - LP must be conducted if blood culture is positive due to increased risk of meningitis; otherwise controversial and depends on clinical presentation

Management

- supportive care
- IV antibiotics: typically ampicillin + cefotaxime or ampicillin + gentamicin chosen as first-line empiric therapy
- choice of antibiotic and duration of treatment dependent on symptoms, culture results, maternal GBS status, and local resistance patterns
- if meningitis suspected, consider IV ampicillin + cefotaxime ± vancomycin at meningitic doses
- addition of IV acyclovir if HSV infection suspected

Skin Conditions of the Neonate

Table 40. Common Neonatal Skin Conditions

Neonatal Skin Condition	Description
Vasomotor Response (Cutis Marmorata, Acrocyanosis)	Transient mottling when exposed to cold; usually normal, particularly if premature
Vernix Caseosa	Soft, creamy, white layer covering baby at birth
Congenital Dermal Melanocytosis	Slate grey patches over lower back, buttocks, and lower limbs (may look like bruises); prevalence varies with ethnicity (Asian > Black > Hispanic > White); typically fades within first 2 yr of life
Capillary Hemangioma	Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yr, 90% by 9 yr
Erythema Toxicum Neonatorum	Yellow-white papules/pustules surrounded by erythema, eosinophils within the lesions; common rash, resolves in 5-7 d
Milia	1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolves within first few weeks of life
Transient Pustular Melanosis	Hyperpigmented macular base with pustules, seen more commonly in Black infants; may be present at birth; no treatment needed
Nevus Simplex (Salmon Patch)	Transient macular vascular malformation of the eyelids and/or neck ("Angel Kiss" or "Stork Bite"); most lesions disappear by 1 yr
Neonatal Acne	Inflammatory papules and pustules mainly on face; self-resolving usually within 4 mo

Nephrology

Common Pediatric Renal Diseases

Table 41. Common Manifestations of Renal Disease

Age	Symptoms	Common Causes
Neonate	Flank Mass	Hydronephrosis, polycystic disease (autosomal dominant or recessive subtypes), tumour
	Hematuria	Renal vein thrombosis, asphyxia, malformation, trauma
	Anuria/Oliguria	Bilateral renal agenesis, obstruction, asphyxia
Child and Adolescent	Cola/Red-Coloured Urine	Acute GN (e.g. post-streptococcal, HSP, IgA nephropathy, etc.), hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis)
	Gross Hematuria	Urologic disease (e.g. nephrolithiasis, trauma, etc.), UTI, acute GN
	Edema	Nephrotic syndrome, nephritis, acute/chronic renal failure, cardiac or liver disease
	Hypertension	GN, renal failure, dysplasia (consider coarctation, drugs, endocrine causes)
	Polyuria	DM, central and nephrogenic DI, renal Fanconi's syndrome (genetic/metabolic/acquired causes), hypercalcemia, polyuric renal failure (renal dysplasia)
	Proteinuria	Orthostatic, nephrotic syndrome (MCD, etc.), GN
	Oliguria	Dehydration, ATN, interstitial nephritis, acute or chronic kidney disease (i.e. renal failure)
	Urgency	UTI, vulvovaginitis

Hemolytic Uremic Syndrome

Definition

- simultaneous occurrence of the triad of:
  1. non-immune microangiopathic hemolytic anemia
  2. thrombocytopenia
  3. acute renal injury

Epidemiology

- annual incidence of 1-2 in 100000 in Canada
- most common cause of acute renal failure in children

Etiology
- STEC-HUS: 90% of pediatric HUS; caused by Shiga toxin-producing *E. coli* (usually O157:H7)
- atypical HUS: 10% of pediatric HUS; caused by hereditary mutations in complement pathway, non-Shiga toxin infections (e.g. S. pneumoniae, HIV), and drugs (cisplatin, oral contraceptives, cyclosporin tacroliumus, and others)

Pathophysiology
- toxin binds, invades, and destroys colonic epithelial cells, causing bloody diarrhea
- toxin enters the systemic circulation, attaches to, and injures endothelial cells (especially in the kidney), causing a release of endothelial products (e.g. von Willebrand factor, platelet aggregating factor)
- platelet/fibrin thrombi form in multiple organ systems (e.g. kidney, pancreas, brain) resulting in thrombocytopenia
- RBCs are forced through occluded vessels, resulting in fragmented RBCs (schistocytes) that are removed by the reticuloendothelial system (hemolytic anemia)

Clinical Features
- initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea; within 5-7 d begins to show signs of anemia, thrombocytopenia, and renal insufficiency
- pallor, jaundice (hemolysis), edema, petechiae, HTN, decreased urine output

Investigations
- CBC (anemia, thrombocytopenia), blood smear (schistocytes), electrolytes (due to fluid loss), renal function, urinalysis (microscopic hematuria), stool cultures, and verotoxin/shigella toxin assay

Management
- mainly supportive: nutrition, hydration, ventilation (if necessary), blood products
- dialysis if symptomatic uremia, refractory electrolyte abnormality (e.g. hyperkalemia), or severe fluid overload
- STEC-HUS: avoid antibiotics, NSAIDs, and antidiarrheal agents; no treatments associated with improved outcomes
- atypical HUS: plasma exchange or eculizumab

Prognosis
- STEC-HUS: <5% mortality rate, 30% develop long-term renal damage (e.g. HTN, proteinuria, decreased GFR)
- atypical HUS: worse prognosis compared to STEC-HUS, 50% of cases result in death or dialysis-dependent renal disease

Nephritic Syndrome

Definition
- acute or chronic syndrome affecting the kidney, characterized by glomerular injury and inflammation
- defined by hematuria (>5 RBCs per high-powered microscope field), presence of dysmorphic RBCs, and RBC casts on urinalysis
- often accompanied by at least one of: proteinuria (<50 mg/kg/d), edema, HTN, azotemia, and oliguria

Epidemiology
- highest incidence in children ages 5-15 yr

Etiology
- humoral immune response to a variety of etiologic agents → immunoglobulin deposition → complement activation, leukocyte recruitment, release of growth factors/cytokines → glomerular inflammation and injury → porous podocytes → hematuria + RBC casts ± proteinuria
- HTN secondary to fluid retention and increased renin secretion by ischemic kidneys

Table 42. Major Causes of Nephritic Syndrome

	Decreased C3	Normal C3
Primary (idiopathic)	Post-infectious GN (streptococcal infection is the most common) Membranoproliferative Type I (50-80%) Type II (>80%)	IgA nephropathy Idiopathic rapidly progressive GN Anti-GBM disease
Secondary (systemic disease)	SLE Bacterial endocarditis Abscess or shunt nephritis Cryoglobulinemia	HSP (very common) Polyarteritis nodosa Granulomatosis with polyangiitis Goodpasture's syndrome

Nephritic Syndrome

PHAROH
Proteinuria (<50 mg/kg/d)
Hematuria
Azotemia
RBC casts
Oliguria
HTN

Clinical Features
- often asymptomatic; some overlap in clinical findings for nephritic and nephrotic syndrome
- gross hematuria, mild-moderate edema, oliguria, HTN
- signs and symptoms suggestive of underlying systemic causes (e.g. fever, arthralgias, rash, dyspnea, pulmonary hemorrhage)

Investigations
- urine
  - dipstick (hematuria, 0 to 2+ proteinuria) and microscopy (>5 RBCs per high-powered microscope field, acanthocytes, RBC casts)
  - first morning urine protein/creatinine ratio (<200 mg/mmol)
- blood work
  - CBC, electrolytes, Cr, BUN, albumin
  - impaired renal function (↑ Cr and BUN) resulting in ↑ pH and electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia)
  - mild anemia on CBC (secondary to hematuria)
  - hypoalbuminemia (secondary to proteinuria)
  - appropriate investigations to determine etiology: C3/C4 levels, serologic testing for recent streptococcal infection (ASOT, anti-hyaluronidase, anti-streptokinase, anti-NAD, anti-DNAse B), ANA, anti-DNA antibodies, ANCA, serum IgA levels, anti-GBM antibodies
- renal biopsy should be considered only in the presence of acute renal failure, no evidence of streptococcal infection, normal C3/C4

Management
- treat underlying cause
- symptomatic
  - renal insufficiency: supportive (dialysis if necessary), proper hydration
  - HTN: salt and fluid restriction (but not at expense of renal function), ACEI or ARBs for chronic persistent HTN (not acute cases because ACEI or ARBs may decrease GFR further)
  - edema: salt and fluid restriction, possibly diuretics (avoid if significant intravascular depletion)
- corticosteroids if indicated: IgA nephropathy, lupus nephritis, etc.
- post-streptococcal GN should be monitored for complications long term (annual BP, urinalysis)

Prognosis
- dependent on underlying etiology
- complications include HTN, heart failure, pulmonary edema, chronic kidney injury (requiring renal transplant)

Nephrotic Syndrome

Definition
- clinical syndrome affecting the kidney, characterized by significant proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia

Nephrotic Syndrome - HELP
Hypoalbuminemia (<20 g/L)
Edema
Lipids elevated
Proteinuria (>50 mg/kg/d)

Epidemiology
- highest incidence in children 2-6 yr, M>F

Etiology
- primary (idiopathic): nephrotic syndrome in the absence of systemic disease (most common cause in pediatrics)
  - glomerular inflammation ABSENT on renal biopsy: MCD (85%), focal segmental glomerulosclerosis
  - glomerular inflammation PRESENT on renal biopsy: membranoproliferative GN, IgA nephropathy
- secondary: nephrotic syndrome associated with systemic disease or due to another process causing glomerular injury (<10% in pediatrics)
  - autoimmune: SLE, DM, juvenile idiopathic arthritis
  - genetic: sickle cell disease, Alport syndrome
  - infections: hepatitis B/C, post-streptococcal, infective endocarditis, HUS, HIV
  - malignancies: leukemia, lymphoma
  - medications: captopril, penicillamine, NSAIDs, antiepileptics
  - vasculitides: HSP, granulomatosis with polyangiitis
- congenital: congenital nephropathy of the Finnish type, Denys-Drash syndrome, etc.

Clinical Features

- edema
  - often first sign; detectable when fluid retention exceeds 3-5% of body weight
  - starts periorbital and often pretibial → edematous areas are white, soft, and pitting
  - gravity dependent: periorbital edema ↓ and pretibial edema ↑ over the day
  - anasarca may develop (i.e. marked periorbital and peripheral edema, ascites, pleural effusions, scrotal/labial edema)
- non-specific symptoms such as irritability, malaise, fatigue, anorexia, or diarrhea
- decrease in effective circulating volume (e.g. tachycardia, HTN, oliguria, etc.)
- foamy urine is a possible sign of proteinuria

Daily protein excretion can be estimated from a random urine protein/creatinine ratio

Investigations

- urine
  - urine dipstick (3 to 4+ proteinuria, microscopic hematuria) and microscopy (oval fat bodies, hyaline casts)
  - first morning urine protein/creatinine ratio (>300 mg/mmol)
- blood work
  - diagnostic: hypoalbuminemia (<25 g/L), hyperlipidemia/hypercholesterolemia (total cholesterol >5 mmol/L)
  - secondary: electrolytes (hypocalcemia, hyperkalemia, hyponatremia), renal function (↑ BUN and Cr), coagulation profile (↓ PTT)
  - appropriate investigations to rule out secondary causes: CBC, blood smear, C3/C4, ANA, hepatitis B/C titres, ASOT, HIV serology, etc.
- consider renal biopsy if: HTN, gross hematuria, ↓ renal function, low serum C3/C4, no response to steroids after 4 wk of therapy, frequent relapses (>2 in 6 mo), presentation before first yr of life (high likelihood of congenital nephrotic syndrome), presentation ≥12 yr (rule out more serious renal pathology than MCD)

Side Effects of Long-Term Steroid Use

GOOD CUSHINGS
Growth impairment
Obesity
Osteoporosis
Dorsal hump

Changes in behaviour
Ulcers
Striae
Hypertension
Immunosuppression; infection
Need to eat
Glucose elevation
Salt and water retention

Management

- MCD: oral prednisone 2 mg/kg/d (or equivalent) for up to 12 wk → varicella status should be known before starting (prednisone can significantly exacerbate infection)
- consider cytotoxic agents, immunomodulators, or high-dose pulse corticosteroid if steroid resistant
- symptomatic
  - edema: salt and fluid restriction, possibly diuretic (avoid if significant intravascular depletion); furosemide + albumin for anasarca
  - hyperlipidemia: generally resolves with remission; limit dietary fat intake; consider statin therapy if persistently nephrotic
  - hypoalbuminemia: IV albumin and furosemide not routinely given; consider if refractory edema
  - abnormal BP: control BP; fluid resuscitation if severe intravascular depletion; ACEI or ARBs for persistent HTN
- diet: no added salt; monitor caloric intake and supplement with Ca^{2+} and vitamin D if on corticosteroids
- daily weights and BP to assess therapeutic progress
- secondary infections: treat with appropriate antimicrobials; antibiotic prophylaxis not recommended; pneumococcal vaccine at diagnosis and varicella vaccine after remission; varicella Ig + acyclovir if exposed while on corticosteroids
- secondary hypercoagulability: mobilize, avoid hemoconcentration due to hypovolemia, prompt sepsis treatment, consider anticoagulation in consultation with Thrombosis if thrombi occur

Prognosis

- generally good: 80% of children respond to corticosteroids
- up to 2/3 experience relapse, often multiple times; sustained remission with normal kidney function usually by adolescence
- complications: ↑ risk of infections (spontaneous peritonitis, pneumonia/empyema, cellulitis, sepsis); hypercoagulability due to decreased intravascular volume and antithrombin III depletion (PE, renal vein thrombosis); intravascular volume depletion, leading to hypotension, shock, renal failure; anasarca; adverse effects on growth; drug side effects

Hypertension in Childhood

Definition
- HTN: sBP and/or dBP ≥95th percentile for sex, age, and height on ≥3 occasions
- elevated BP (formerly pre-HTN): sBP and/or dBP ≥90th percentile but <95th percentile or BP ≥120/80 irrespective of age, sex, and height

Table 43. 95th Percentile Blood Pressures (mmHg)

	Female		Male	
Age (Yr)	**50th Percentile for Height**	**75th Percentile for Height**	**50th Percentile for Height**	**75th Percentile for Height**
1	103/60	104/61	103/55	104/56
6	111/72	112/73	111/71	112/72
12	122/78	124/79	121/78	124/78
17	127/81	128/82	135/85	137/86

Flynn JT, Kaelber DC, Baher-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140(3):e20171904

Epidemiology
- prevalence: 3-5% for HTN, 7-10% for elevated BP; M>F

Etiology
- primary HTN
  - diagnosis of exclusion
  - most common in older children (≥10 yr), especially if positive family history, overweight, and only mild HTN
  - responsible for ~90% of cases of HTN in adolescents, rarely in young children
- secondary HTN
  - identifiable cause of HTN (most likely etiology depends on age)
  - responsible for majority of childhood HTN
- always consider white coat HTN for all ages and use of an appropriate BP cuff size

Table 44. Etiology of HTN by Age Group

System	Neonates	1 mo-6 yr	7-12 yr	>13 yr
Endocrine/Metabolic	CAH	Wilms' tumour (↑ renin) Neuroblastoma (↑ catecholamines)	Endocrinopathies* Essential hypertension	Endocrinopathies* Essential hypertension
Renal	Congenital renal disease Renal artery thrombosis	Renal parenchymal disease	Renal parenchymal disease	Renal parenchymal disease
Vascular	Coarctation of the aorta Renal artery thrombosis	Coarctation of the aorta RAS	Renovascular abnormalities	Renovascular disease
Drugs		Corticosteroids Cyclosporine and tacrolimus	Corticosteroids OCP Cyclosporine and tacrolimus	Corticosteroids OCP Cyclosporine and tacrolimus Recreational drugs (amphetamines, cocaine, etc.)

*Note: may include hyperthyroidism, hyperparathyroidism, Cushing's syndrome, primary hyperaldosteronism/Conn's syndrome, pheochromocytoma

Risk Factors
- primary HTN: obesity, male sex, African ethnicity, family history of HTN, LBW
- secondary HTN: prepubertal age, no family history of HTN, history of renal disease, family history of autoimmune disease

Clinical Features
- often asymptomatic, but can include FTT, fatigue, epistaxis
- symptoms of hypertensive emergency
  - neurologic: headache, seizures, focal complaints, change in mental status, visual disturbances
  - cardiovascular: symptoms of MI or heart failure (chest pain, palpitations, cough, SOB)
- symptoms of secondary HTN: guided by etiology; ask about medications and recreational drugs (current and past)

Investigations
- physical exam: upper and lower limb BP with correct cuff size, BMI, full neurologic exam, ophthalmoscopy, precordial exam, peripheral pulses, perfusion status

Signs of Secondary HTN
- Edema (renal parenchymal disease)
- Abdominal or renal bruit (RAS)
- Differential 4 limb BP/diminished femoral pulses (coarctation)
- Abdominal mass (Wilms', neuroblastoma)
- Goitre/skin changes (hyperthyroidism)
- Ambiguous genitalia (CAH)

Pediatric BP Calculation
sBP= age x 2 + 90
dBP= 2/3 x sBP

- laboratory
  - BUN, creatinine, electrolytes, urinalysis, fasting lipid profile
  - obese patients: HbA1c, AST, ALT
  - further investigations based on history and physical
- imaging: renal ultrasound (with doppler), echo (coarctation, LVH)
- 24 h ambulatory blood pressure monitoring (if assessing white coat HTN)

Management
- treat underlying cause
- non-pharmacologic: modify concurrent cardiovascular risk factors (e.g. weight reduction, exercise, salt restriction, smoking and recreational drug use cessation)
- pharmacologic: gradual lowering of BP using thiazide diuretics; no antihypertensives have been formally studied in children; if hypertensive emergency use hydralazine, labetalol, sodium nitroprusside
- investigation and management of end-organ damage (e.g. retinopathy, LVH)
- consider referral to specialist Pediatrician or Pediatric Nephrologist

Prognosis
- end-organ damage (similar to adults) including LVH, CHF, cerebrovascular insults, renal disease, retinopathy

Neurology

Cerebral Palsy

Definition
- non-progressive central motor impairment syndrome due to CNS anomaly or neural injury at the prenatal, perinatal, or postnatal stage
- incidence: 1.5-2.5 in 1000 live births (industrialized nations)
- life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion

Etiology
- no known cause identified in 1/3 of cases
- prenatal causes: TORCH infections, maternal disorders (e.g. epilepsy), congenital CNS anomaly
- perinatal causes: prematurity, LBW, ischemic stroke
- postnatal causes: infections (e.g. meningitis), asphyxia, IVH, trauma, severe jaundice

Clinical Features
- general signs: delay in motor milestones, developmental delay, learning disabilities, visual/hearing impairment, seizures, microcephaly, uncoordinated swallow (aspiration)

Table 45. Types of Cerebral Palsy

Type	Characteristics	Area of Brain Involved
Spastic (70-80%)	Truncal hypotonia in first yr Increased tone, increased reflexes, clonus Can affect one limb (monoplegia), one side of body (hemiplegia), both legs (diplegia), or both arms and legs (quadriplegia)	UMN of pyramidal tract Hemiplegia most commonly caused by middle cerebral artery stroke Diplegia associated with periventricular leukomalacia in premature babies Quadriplegia associated with HIE (asphyxia), higher incidence of intellectual disability
Athetoid/Dyskinetic (10-15%)	Athetosis ± chorea or hypotonia Can involve face, tongue (results in dysarthria)	Basal ganglia (may be associated with kernicterus)
Ataxic (<5%)	Poor coordination, poor balance (wide based gait) Can have intention tremor	Cerebellum
Mixed (10-15%)	More than one of the above motor patterns	Some combination of the above

Investigations
- neuroimaging (MRI), may include metabolic screen, chromosome studies, serology, EMG, EEG (if seizures), ophthalmology assessment, audiology assessment

Management
- maximize potential through multidisciplinary services (e.g. primary care physician, OT, PT, SLP, school supports, etc.)
- orthopedic and/or neurosurgical management (e.g. dislocations, contractures, rhizotomy)
- management of symptoms: spasticity (baclofen, Botox®), constipation (stool softeners)

Febrile Seizures

Epidemiology
- most common cause of seizures in children (3-5% of children)
- M>F; age 6 mo-6 yr

Clinical Features
- otherwise well, neurotypical child
- fever often with associated illness (source of fever), family history, past history of simple febrile seizures
- no evidence of CNS infection/inflammation before or after seizure; no history of non-febrile seizures

Table 46. Comparison of Typical and Atypical Febrile Seizures

Simple/Typical (70-80%)	Complex/Atypical (20-30%)
All of the following: Duration <15 min (95% <5 min) Generalized tonic-clonic No recurrence in 24 h period No neurological impairment or developmental delay before or after seizure Very small risk of developing epilepsy (2% vs. 1% in general population)	At least one of the following: Duration >15 min Focal onset or focal features during seizure Recurrent seizures (>1 in 24 h period) Previous neurological impairment or neurological deficit after seizure Increased risk of developing epilepsy

Investigations
- history: determine focus of fever, description of seizure, medications, trauma history, developmental history, FMHx
- physical exam: LOC, signs of meningitis, neurological exam, head circumference, focus of infection
- septic workup including LP if suspecting meningitis (strongly consider if child <12 mo; consider if child is 12-18 mo; only if meningeal signs present in child >18 mo)
- if typical febrile seizure, investigations only for determining focus of fever, no LP done if child regained baseline and is well
- EEG/CT/MRI brain not warranted unless atypical febrile seizure or abnormal neurologic findings

Management
- counsel and reassure patient and parents
  - febrile seizures do not cause brain damage
  - very small risk of developing epilepsy in simple febrile seizures
  - 33% chance of recurrence (mostly within 1 yr of first seizure and in children <1 yr)
- antipyretics and fluids for comfort (though neither prevent seizure)
- no prophylaxis with antiepileptic drugs
- if high-risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home
- treat underlying cause of fever

Causes of Hypotonia that Respond to Rapid Treatment

H4I2SAD
Hypokalemia
Hypermagnesemia
Hypoglycemia
Hydrocephalus
Infection
ICH
Seizure
Acidemia
Drugs/toxins

Hypotonia

Definition
- decreased resistance to passive movements – "floppy baby"

Differential Diagnosis
- central: genetic (DS, Prader-Willi, Fragile X syndrome), metabolic (hypoglycemia, kernicterus), perinatal problems (HIE, ICH), endocrine (hypothyroidism, hypopituitarism), systemic illness (TORCH infection, sepsis, dehydration), CNS malformations, dysmorphic syndromes
- peripheral: motor neuron (spinal muscular atrophy, polio), peripheral nerve (Charcot-Marie-Tooth syndrome), neuromuscular junction (myasthenia gravis), muscle fibre (mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

Clinical Features
- history: GA, onset/progression, family history of neuromuscular abnormalities, obstetrical history, birth trauma
- physical exam:
  - general: dysmorphic features, weight, length, head circumference
  - MSK: postural movements including traction response, axillary suspension, ventral suspension (see *Figure 17*)
  - neurological: spontaneous posture, muscle bulk, presence of fasciculations
    - UMN lesion (60-80%): increased deep tendon reflexes and clonus; floppy and strong; + Babinski; neonatal reflexes present
    - LMN lesion (15-30%): lack of deep tendon reflexes; floppy and weak; - Babinski; neonatal reflexes absent

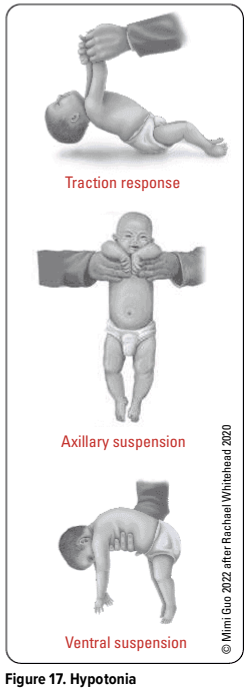


Figure 17. Hypotonia

Investigations
- rule out systemic disorders (e.g. electrolytes, ABG, blood glucose, CK, and serum/urine investigations for multiple etiologies including mitochondrial causes)
- neuroimaging: MRI/MRA when indicated
- EMG, muscle biopsy/NCS
- chromosome analysis, genetic testing, metabolic testing, neuromuscular testing, subspecialty consultations

Management
- depends on etiology: some treatments available for specific diagnosis
- counsel parents on prognosis and genetic implications
- refer patients for specialized care including: rehabilitation, OT, PT, assess feeding ability

Neurocutaneous Syndromes

Definition
- characterized by skin colour changes and tendency to form tumours of the CNS, PNS, viscera, and skin

In neurocutaneous syndromes, the younger the child at presentation, the more likely they are to develop intellectual disability

NEUROFIBROMATOSIS TYPE I (VON RECKLINGHAUSEN DISEASE)
- autosomal dominant but 50% are the result of new mutations
- incidence 1 in 3000, mutation in NF1 gene on 17q11.2 (codes for neurofibromin protein)
- learning disorders, abnormal speech development, and seizures are common
- diagnosis of NF-1 requires 2 or more of:
  - ≥6 café-au-lait spots (>5 mm if prepubertal, >1.5 cm if postpubertal)
  - ≥2 neurofibromas of any type or one plexiform neurofibroma
  - ≥2 Lisch nodules (hamartomas of the iris)
  - optic glioma
  - freckling in the axillary or inguinal region
  - a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
  - a first degree relative with confirmed NF-1
- management involves monitoring through regular checks of organs (ex optho exam, BP), treatment of disease manifestations as they occur, as well as genetic counselling, OT, PT, and speech therapy as needed

NEUROFIBROMATOSIS TYPE II
- autosomal dominant but >50% are the result of new mutations
- incidence 1 in 33000, mutation in NF2 gene on chromosome 22 (codes for merlin protein)
- characterized by predisposition to form intracranial, spinal tumours
- diagnosed when (a) bilateral vestibular schwannomas are found, OR (b) patient has a first-degree relative with NF-2 AND EITHER unilateral vestibular schwannoma OR any two of the following: meningioma, glioma, schwannoma, neurofibroma, posterior subcapsular lenticular opacities
- treatment consists of monitoring for tumour development and surgery

Recurrent Headache

- see Neurology, N46

Headache – Red Flags
- First and worst headache of their life
- Sudden onset
- Focal neurological deficits
- Constitutional symptoms
- Worse in morning
- Worse with bending over, coughing, straining, supine
- Change in LOC
- Sudden mood changes
- Pain that wakes patient
- Fatigue
- Affecting school attendance

Differential Diagnosis
- primary headache: tension, migraine, cluster
- secondary headache: see Neurology, N46
- anxiety or life stress (e.g. recent move, bullying, parents' divorce, domestic abuse)

General Assessment
- if unremarkable history and physical exam, most likely diagnosis is migraine or tension headache
- CT or MRI if red flags present
- inquire about level of disability, academic performance, after-school activities

Seizure Disorders

- see Neurology, N18

Heart problems, such as long QT syndrome and hypertrophic cardiomyopathy, are often misdiagnosed as epilepsy. Include cardiac causes of syncope in your differential diagnosis, particularly when the episodes occur during physical activity

Differential Diagnosis of Seizures in Children
- benign febrile seizure
- CNS: infection, tumour, HIE, trauma, hemorrhage
- acute metabolic: hypoglycemia, hypocalcemia, hyponatremia
- inborn errors of metabolism
- idiopathic epilepsy and epileptic syndromes
- others: neurocutaneous syndromes, AVM, drug ingestions/withdrawal
- seizure mimics

Investigations
- lab tests: CBC, electrolytes, calcium, magnesium, glucose, phosphate, ± ABG, lactate, ammonia
- toxicology screen
- EEG
- CT/MRI if indicated (focal neurological deficit or has not returned to baseline several hours after seizure)
- consider LP only if suspecting meningitis/encephalitis

Seizure Mimics
- Benign paroxysmal vertigo
- Breath holding
- Hypoglycemia
- Narcolepsy
- Night terror
- Pseudoseizure
- Syncope
- TIA
- Tic

CHILDHOOD EPILEPSY SYNDROMES

Infantile Spasms
- pediatric emergency as can lead to developmental regression in previously well child and therefore must be identified and investigated early
- brief, repeated symmetric contractions of neck, trunk, and extremities (flexion and extension) lasting 10-30 s
- occur in clusters; often associated with developmental delay; onset 4-8 mo
- 20% unknown etiology (usually good response to treatment); 80% due to metabolic or developmental abnormalities, encephalopathies, or associated with neurocutaneous syndromes (usually poor response to treatment)
- can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hypsarrhythmia) or Lennox-Gastaut (see below)
- typical EEG: hypsarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
- management: corticosteroids, vigabatrin, benzodiazepines

Ketogenic Diet and Other Dietary Treatments for Epilepsy
Cochrane DB Syst Rev 2012;3:CD001903
Purpose: Systematic review of all studies of ketogenic and related diets. Included the review of 4 RCTs, 6 prospective studies, and 5 retrospective studies.
Population: Adults and children with diagnosed epilepsy of any type.
Intervention: Ketogenic diet, control (placebo diet, any treatment with known antiepileptic properties). Main Outcome Measure: Seizure control at 3, 6, 12 mo.
Results: Studies showed a response rate of at least 38-50% seizure reduction at 3 mo. This response was maintained for up to a year. A range of side effects were reported. The most frequent were gastrointestinal effects (30%).
Conclusion: The ketogenic diet is a valid option for people with medically-intractable epilepsy.

Lennox-Gastaut
- characterized by triad of:
  1. multiple seizure types
  2. diffuse cognitive dysfunction
  3. slow generalized spike and slow wave EEG
- onset commonly 3-5 yr
- seen with underlying encephalopathy and brain malformations
- management: valproic acid, benzodiazepines, vagal nerve stimulator, and ketogenic diet; however, response often poor

Juvenile Myoclonic Epilepsy (Janz Syndrome)
- myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
- adolescent onset (12-16 yr); autosomal dominant with variable penetrance
- typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
- management: lifelong treatment (valproic acid); excellent prognosis

Childhood Absence Epilepsy
- multiple daily absence seizures lasting <30 s without postictal state that may resolve spontaneously or become generalized in adolescence
- peak age of onset 6-7 yr, F>M, strong genetic predisposition
- typical EEG: 3 Hz spike and wave
- management: valproic acid or ethosuximide

Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes (BECTS)
- focal motor seizures involving tongue, mouth, face, and upper extremity usually occurring in sleep-wake transition states; remains conscious, but aphasic postictally
- onset peaks at 5-10 yr; 16% of all non-febrile seizures; remits spontaneously in adolescence without sequelae
- typical EEG: repetitive spikes in centrotemporal area with normal background
- management: frequent seizures controlled by carbamazepine, no medication if infrequent seizures

General Approach to Treatment
- education for patient and parents including education and precautions in daily life (e.g. buddy system, showers instead of baths)
- medication
  - initiate: treat with drug appropriate to seizure type; often if >2 unprovoked afebrile seizures within 6-12 mo
  - optimize: start with one drug and increase dosage until seizures controlled
  - if no effect, switch over to another before adding a second antiepileptic drug
- continue antiepileptic drug therapy until patient free of seizures for >2 yr, then wean over 4-6 mo
- ketogenic diet (high fat diet): used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

Generalized and Partial Seizures
- see Neurology, N19

Respirology

Asthma

Definition
- see Respirology, R7
- inflammatory disorder of the airways characterized by recurrent episodes of reversible small airway obstruction resulting from airway hyperresponsiveness to endogenous and exogenous stimuli
- in Canada, the lifetime prevalence in childhood is 10-15% and presents most often in early childhood
- associated with other atopic diseases such as allergies and/or atopic dermatitis

Clinical Features
- episodic bouts of wheezing, dyspnea, tachypnea, cough (usually at night/early morning, with activity, or with cold exposure)
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze, or 'quiet'/tight chest when airflow is limited
- symptoms may be exacerbated by "triggers": URTI (viral or *Mycoplasma*), weather (e.g. cold exposure, humidity changes), allergens (e.g. pets), irritants (e.g. cigarette smoke), exercise, emotional stress, drugs (e.g. ASA, β-blockers)
- consider asthma in ages 1-5 y if there are recurrent asthma-like symptoms, even if triggered by viral infection; diagnosis requires documentation of airflow obstruction, reversibility with asthma therapy, and no suspicion of alternative diagnosis

Classification
- mild: occasional attacks of wheezing or coughing (<2/wk); symptoms respond quickly to inhaled bronchodilators alone and seldom need inhaled corticosteroids
- moderate: more frequent episodes with persistent symptoms and chronic cough; decreased exercise tolerance; requires inhaled bronchodilator and inhaled corticosteroids; sometimes needs systemic corticosteroids
- severe: daily and nocturnal symptoms; frequent ED visits and hospitalizations; usually needs systemic corticosteroids
- PRAM score is used in several emergency departments to estimate severity (mild 0-3, moderate 4-7, severe 8-12)

Management
- acute
  - O_2 (keep O_2 saturation >92%) and fluids if dehydrated
  - β2-agonists: salbutamol (Ventolin®) MDI + spacer (nebulized or IV in very severe episodes with impending respiratory failure), 5 puffs (<20 kg) or 10 puffs (>20 kg) q20 min x 3 doses
  - ipratropium bromide (Atrovent®) if severe: MDI + spacer, 4 puffs (<30kg) or 8 puffs (≥30kg) q15-20 min x 3 doses
  - steroids: prednisone (1-2 mg/kg/d x5 d) or dexamethasone (0.6 mg/kg/d x2 d more commonly or 0.3 mg/kg/d x5 d); in severe disease, use IV steroids
  - if no response, add magnesium sulphate
  - continue to observe; can discharge patient if expected β2-agonist need not greater than every 4 hours, $SpO_2 \geq 92\%$ in room air, improved air entry, and minimal work of breathing and PRAM ≤3 sustained for 2-4 h after last bronchodilator dose
  - discharge home with inhaled corticosteroids (12 wk course; e.g. fluticasone)
- chronic
  - education, emotional support, avoid triggers, develop an "action plan", exercise program (e.g. swimming)
  - monitor respiratory function with peak flow metre (improves self-awareness of status)
  - reliever therapy: short acting β2-agonists (e.g. salbutamol)
  - controller therapy (first line therapy for all children): low dose daily inhaled corticosteroids
  - second line therapy for children <12 yr: moderate dose of daily inhaled corticosteroids
  - second line therapy for children >12 yr: leukotriene receptor antagonist OR long acting β2-agonist in conjunction with low dose inhaled corticosteroids; leukotriene receptor antagonist monotherapy may be considered an alternative second line therapy
  - severe asthma unresponsive to first and second line treatments: injection immunotherapy
  - aerochamber for children using daily inhaled corticosteroids
- indications for hospitalization
  - ongoing need for supplemental O_2
  - persistently increased work of breathing
  - β2-agonists are needed more often than q4 h after 4-8 h of conventional treatment
  - patient deteriorates while on systemic steroids

Recommended use of Palivizumab to Reduce Complications of RSV Infection in Infants
Public Health Agency of Canada 2022, Summary of Recommendations for Palivizumab:
Premature infants of <30 wk gestational age (wGA) and <6 mo of age at onset of or during the RSV season.
Children aged <24 mo with chronic lung disease of prematurity who require ongoing oxygen therapy within the 6 mo preceding or during the RSV season
Infants aged <12 mo with hemodynamically significant CHD.
Infants born at <36 wGA and age <6 mo old living in remote northern Inuit communities.

Palivizumab for Preventing Severe RSV Infection in Children
Cochrane Database Syst Rev 2021;11(11):CD013757
Purpose: To assess the effects of palivizumab for preventing severe RSV infection in children.
Methods RCTs (n=5) comparing palivizumab at a dose of 15 mg/ kg once a month with placebo, no intervention or standard of care in children 0 to 24 mo.
Results: Palivizumab reduces hospitalisation due to RSV infection at two years' follow-up (RR 0.44, 95% CI 0.30 to 0.64). The drug results in little to no difference in mortality at two years' follow-up (RR 0.69, 95% CI 0.42 to 1.15), and results in little to no difference in adverse events at 150 days' follow up (RR 1.09, 95% CI 0.85 to 1.39).
Conclusions: Prophylaxis with palivizumab reduces hospitalizations due to RSV infection and results in little to no difference in mortality or adverse events.

Canadian Pediatric Asthma Consensus Guidelines for Assessing Adequate Control of Asthma
CMAJ 2005;173(6 Suppl):S12-14
Daytime symptoms ≤2 d/wk
Night time symptoms <1 night/wk and mild
Normal physical activity
Mild and infrequent exacerbations
No work/school absenteeism
Need for β-agonist ≤2 doses per wk
FEV_1 or peak expiratory flow ≥90% of personal best
Peak expiratory flow diurnal variation <10-15%

Bronchiolitis

Definition
- LRTI, usually in children <2 yr, that has wheezing and signs of respiratory distress

Epidemiology
- the most common LRTI in infants, affects 50% of children in first 2 yr of life; peak incidence at 6 mo, winter or early spring
- increased incidence of asthma later in life

Etiology
- RSV (>50%), parainfluenza, influenza, rhinovirus, adenovirus, M. pneumoniae (rare)

Clinical Features
- usually presents as the first episode of wheeze in children <1 y of age
- prodrome of URTI with cough and/or rhinorrhea, possible fever
- feeding difficulties, irritability
- wheezing, crackles, respiratory distress, tachypnea, tachycardia, retractions, poor air entry; symptoms often peak at 3-4 d

Investigations
- routine investigations are not required when bronchiolitis is suspected (Choosing Wisely)
- CXR (only in poor response to therapy or atypical disease): air trapping, peribronchial thickening, atelectasis, increased linear markings

Management
- self-limiting disease with peak symptoms usually lasting 2-3 wk
- mild to moderate distress
  - supportive: PO or IV hydration, oral/nasal suctioning as needed, antipyretics for fever, regular or humidified high flow O_2
- severe distress
  - as above ± humidified high flow O_2 or intubation and ventilation as needed
  - consider palivizumab (targets F-glycoprotein of RSV) as a prophylaxis in high-risk infants: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodeficient
- bronchodilators, corticosteroids, and antibiotics have no therapeutic value (unless there is secondary bacterial pneumonia)
- indications for hospitalization
  - hypoxia: O_2 saturation <92% on initial presentation or increasing O_2 requirements
  - signs of severe distress (tachypnea >80/min, tachycardia >180/min, grunting, nasal flaring, marked chest retractions, lethargy) despite several salbutamol masks
  - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
  - high-risk infants: history of prematurity (<34 wk), weight <4 kg, age <7 wk
  - significant feeding problems
  - socioeconomic barriers to improvement (e.g. inadequate care at home)

Bronchodilators for Bronchiolitis
Cochrane DB Syst Rev 2010;12:CD001266
Purpose: To assess the effects of bronchodilators in infants with acute bronchiolitis.
Methods: Meta-analysis of placebo-controlled RCTs evaluating bronchodilators for bronchiolitis. Oxygen saturation was the main outcome.
Results: 30 trials with 1992 infants with bronchiolitis were included. Oxygen saturation did not improve with bronchodilators (mean difference (MD) -0.43, 95% CI -0.92 to 0.06). Neither outpatient (11.9% vs. 15.9%, OR 0.75, 95% CI 1.21) nor inpatient (MD 0.06, 95% CI -0.27 to 0.39) reduced hospitalization rates. Effects on oximetry seen in inpatients (MD -0.62, 95% CI -1.40 to 0.16) were slightly larger than for outpatients (MD -0.25, 95% CI -0.61 to 0.11). No change in average clinical score was seen in inpatients (standardized MD -0.14, 95% CI -0.41 to 0.12), while a statistically significant decrease was seen in outpatients (MD -0.42, 95% CI -0.79 to -0.06). Adverse events included tachycardia, oxygen desaturation, and tremors.
Conclusions: Bronchodilators do not improve oxygen saturation, rates of hospital admission, duration of hospitalizations, or durations to resolution of illness. They are not considered effective in routine management of bronchiolitis, especially given their adverse effects.

Children with bronchiolitis do not respond to salbutamol, ipratropium bromide (Atrovent®), or steroids

Cystic Fibrosis

- see Respirology, R12

Etiology
- 1 in 3000 live births, most common in people of Northern European descent
- autosomal recessive, mutation in CFTR gene found on chromosome 7 (ΔF508 mutation in 70%, but >1600 different mutations identified) resulting in a dysfunctional chloride channel on the apical membrane of cells
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction

Clinical Features
- neonatal: meconium ileus, prolonged jaundice, antenatal bowel perforation
- infancy: pancreatic insufficiency with steatorrhea and FTT (despite voracious appetite), anemia, hypoproteinemia, hyponatremia
- childhood: heat intolerance, wheezing or chronic cough, recurrent chest infections (*S. aureus, P. aeruginosa, H. influenzae*), hemoptysis, nasal polyps, distal intestinal obstruction syndrome, rectal prolapse, clubbing of fingers
- older patients: COPD, infertility (males), decreased fertility (female)

Investigations
- neonatal screening
- sweat chloride test x 2 (>60 mEq/L)
  - false positive tests: malnutrition, atopic dermatitis, hypothyroidism, hypoparathyroidism, GSD, adrenal insufficiency, G6PD deficiency, Klinefelter syndrome, technical issues, autonomic dysfunction, familial cholestasis syndrome
  - false negative tests: technical problem with test, malnutrition, skin edema, mineralocorticoids

CF Presenting Signs

CF PANCREAS
Chronic cough and wheezing
FTT
Pancreatic insufficiency (symptoms of malabsorption such as steatorrhea)
Alkalosis and hypotonic dehydration
Neonatal intestinal obstruction (meconium ileus)/Nasal polyps
Clubbing of fingers/Chest radiograph with characteristic changes
Rectal prolapse
Electrolyte elevation in sweat, salty skin
Absence or congenital atresia of vas deferens
Sputum with S. aureus or P. aeruginosa (mucoid)

- CFTR gene mutation analysis: genetic screening panels or gene sequencing if clinically suspicious for rare mutation, useful when sweat chloride test is equivocal
- disease often detected during newborn genetic screening; positive result requires DNA testing and subsequent sweat chloride testing

Management
- nutritional counselling: high calorie diet, pancreatic enzyme replacements, fat soluble vitamin supplements
- management of chest disease: physiotherapy, postural drainage, exercise, bronchodilators, aerosolized DNase and inhaled hypertonic saline, antibiotics (e.g. cephalosporin, cloxacillin, ciprofloxacin, inhaled tobramycin depending on sputum C&S), lung transplantation
- genetic counselling

Complications
- respiratory failure, pneumothorax (poor prognostic sign), cor pulmonale (late), pancreatic fibrosis with DM, gallstones, cirrhosis with portal HTN, infertility (male), recurrent respiratory infections
- early death (current median survival in Canada is 46.6 yr)

Pneumonia

Etiology
- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

Clinical Features
- incidence is greatest in first year of life with viral causes being most common in children <5 yr
- fever, cough, tachypnea
- CXR: diffuse, streaky infiltrates bilaterally
- bacterial causes may present with cough, fever, chills, dyspnea, more dramatic CXR changes (e.g. lobar consolidation, pleural effusion)

Management
- supportive therapy: hydration, antipyretics, humidified O_2

Table 47. Common Causes and Treatment of Community-Acquired Pneumonia

Age	Bacterial	Viral	Treatment
Neonates	GBS *E. coli* *Listeria*	HSV CMV Enterovirus	Ampicillin AND gentamicin
1-3 mo	*S. aureus* *S. pneumoniae* *Chlamydia trachomatis* *H. influenzae*	RSV Influenza Human metapneumovirus Adenovirus Parainfluenza virus	Ampicillin OR ceftriaxone Azithromycin (if *Chlamydia trachomatis* suspected)
3 mo-5 yr	*S. pneumoniae* *S. aureus* *S. pyogenes*	RSV Influenza Human metapneumovirus Adenovirus Parainfluenza virus	High dose amoxicillin OR ampicillin OR ceftriaxone
>5 yr	*S. pneumoniae* *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *S. aureus* *H. influenzae*	Influenza	High dose amoxicillin OR ampicillin OR ceftriaxone Azithromycin OR clarithromycin (if *Mycoplasma/Chlamydophila pneumoniae* suspected)

Note: for severe pneumonia with/without effusion, add Vancomycin for rapidly progressing multilobar disease or pneumatoceles

Respiratory Distress

DYSPNEA

Definition
- any sensation of a difficulty in breathing

Approach
- determine if patient is sick or not sick; ABCs
- history: onset, previous episodes, precipitating events, associated symptoms, past medical/family history of respiratory disease
- physical exam: vitals, SpO_2, evidence of cyanosis, respiratory, cardiovascular
- investigations: CBC and differential, electrolytes, BUN, Cr, NP swab, ABG, CXR, ECG (based on clinical findings)

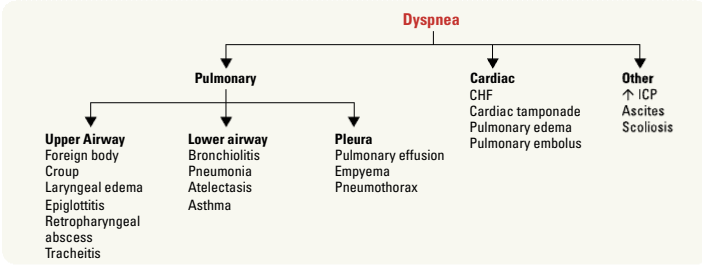


Figure 18. Approach to dyspnea in childhood

WHEEZING

Definition

- a whistling sound that can occur when breathing, mainly during expiration
- caused by obstruction of airways below thoracic inlet

Differential Diagnosis of Wheezing

- common: asthma (recurrent wheezing episodes, identifiable triggers, typically >6 yr), bronchiolitis (first episode of wheezing, usually <1 yr), recurrent aspiration (often neurological impairment), pneumonia (fever, cough, malaise)
- uncommon: foreign body (acute unilateral wheezing and coughing), CF (prolonged wheezing, unresponsive to therapy), bronchopulmonary dysplasia (often develops after prolonged ventilation in the newborn)
- rare: CHF, mediastinal mass, bronchiolitis obliterans, tracheobronchial anomalies

STRIDOR

Definition

- a noisy, high-pitched sound that can occur when breathing
- caused by obstruction above the thoracic inlet and may also present with hoarseness and suprasternal retractions
- stridor at rest is an emergency

Differential Diagnosis of Stridor

- croup, bacterial tracheitis, epiglottitis, foreign body aspiration, subglottic stenosis (congenital or iatrogenic), laryngomalacia/tracheomalacia (collapse of airway cartilage on inspiration), retropharyngeal abscess

Table 48. Common Upper Respiratory Tract Diseases in Children

	Croup (Laryngotracheitis)	Bacterial Tracheitis	Epiglottitis	Choanal Atresia
Affected Site	Subglottis	Trachea	Supraglottis	Posterior nasal aperture(s)
Epidemiology	Common in children 6-36 mo Increased incidence in fall and winter months	Rare Usually seen in children 3 mo to 6 yr	Decreased incidence due to Hib vaccination Common in children 2-6 yr	1 in 7000 live births 2 in 3 are unilateral F>M
Etiology	Parainfluenza (75%) Influenza A and B RSV Adenovirus	*S. aureus* *S. pneumoniae* *H. influenzae* α-hemolytic *Strep* *M. catarrhalis*	*H. influenzae* *S. pneumoniae* β-hemolytic Strep *S. aureus*	Oronasal membrane persists preventing the nose joining the oropharynx
Clinical Presentation	Non-toxic appearance Barking cough Stridor Viral prodrome (rhinorrhea, pharyngitis, cough ± low-grade fever) Hoarseness	Toxic appearance Rapid progression Cough Biphasic stridor No response to corticosteroids and nebulized epinephrine	Toxic appearance Rapid progression 4 **D**s: **d**rooling, **d**ysphagia, **d**ysphonia, **d**istress Stridor Tripod position No cough Fever (>39°C)	Unilateral: diagnosed later in life, unilateral discharge or obstruction Bilateral: diagnosed during infancy, noisy breathing, cyanosis that worsens with feeds and improves when crying
Investigations	Clinical diagnosis CXR: "steeple sign" from subglottic narrowing	Clinical diagnosis Endoscopy: definitive diagnosis	Clinical diagnosis Perform physical exam cautiously to avoid exacerbating respiratory distress	Inability to pass NG tube through nares CT: definitive diagnosis
Management	Mild-to-moderate: corticosteroids, supportive care Severe: corticosteroids, nebulized epinephrine, humidified oxygen, intubation if necessary	Intubation IV antibiotics	Intubation IV antibiotics	Acute (bilateral choanal atresia): place oral airway, initiate gavage feedings Long-term: referral to otolaryngology

Rheumatology

Growing Pains

Epidemiology
- age 2-12 yr, M=F

Clinical Features
- diagnosis of exclusion
- intermittent, non-articular pain in childhood with normal physical exam findings
- pain at night, often bilateral and limited to the calf, shin, or thigh; typically short-lived
- relieved by heat, massage, mild analgesics
- child is well, asymptomatic during the day, no functional limitations
- possible family history of growing pains

Management
- lab investigations not necessary if typical presentation; reassurance and supportive management

Juvenile Idiopathic Arthritis

- a heterogenous group of conditions characterized by persistent arthritis in children <16 yr
- diagnosis: arthritis in ≥1 joint(s); duration ≥6 wk; onset age <16 yr; exclusion of other causes of arthritis; classification defined by features/number of joints affected in the first 6 mo of onset

Systemic Arthritis (Still's Disease)
- onset at any age, M=F
- once or twice daily fever spikes (>38.5°C) ≥2 d/wk with temperature returning rapidly to baseline; children usually acutely unwell during fever episodes
- extra-articular features: erythematous "salmon-coloured" maculopapular rash, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia, serositis, pericarditis
- arthritis may occur wk to mo later
- high ESR, CRP, WBC, platelet count

Oligoarticular Arthritis (1-4 joints)
- most common type of JIA
  - onset early childhood (<5 yr), F>M
- persistent: affects no more than 4 joints during the disease course
- extended: affects more than 4 joints after the first 6 mo
- typically affects large joints: knees (most common), ankles, elbows, wrists; hip involvement unusual
- ANA positive ~60-80%, RF negative
- screening eye exams for asymptomatic anterior uveitis (occurs in ~30%)
- complications: knee flexion contracture, quadriceps atrophy, leg-length discrepancy, growth disturbances, uveitis

Polyarticular Arthritis (5 or more joints)
- ANA positive in 50%, uveitis in 10%
- RF negative (more common)
  - onset: 2-4 yr and 6-12 yr, F>M
  - symmetrical involvement of large and small joints of hands and feet, TMJ, cervical spine
- RF positive
  - onset: late childhood/early adolescence, F>M
  - similar to the aggressive form of adult rheumatoid arthritis and has a similar course progressing into adulthood in most cases
  - severe, rapidly destructive, symmetrical arthritis of large and small joints
  - may have rheumatoid nodules at pressure points (elbows, knees)

Enthesitis-Related Arthritis
- onset: late childhood/adolescence, M>F
- RF negative arthritis and/or enthesitis (inflammation at the site where tendons or ligaments attach to the bone)
- weight bearing joints, especially hip and intertarsal joints, or sacroiliitis
- risk of developing ankylosing spondylitis in adulthood
- asymmetric involvement of lower limb joints, associated with HLA-B27 and development of symptomatic uveitis/iritis

Psoriatic Arthritis
- onset: 2-4 yr and 9-11 yr, F>M
- arthritis and psoriasis OR arthritis and at least two of:
  - dactylitis, nail pitting or other abnormalities, or family history of psoriasis in a 1st degree relative
  - asymmetric or symmetric small or large joint involvement (usually knees and small joints in the hands and feet)
- erythematous, scaly lesions on scalp, post-auricular area, peri-umbilicus, or over extensor surfaces of elbows and knees

Management
- goals of therapy: eliminate inflammation, prevent joint damage, promote normal growth and development as well as normal function, minimize medication toxicity
- moderate-intensity exercise (aerobic fitness, flexibility exercises, and strengthening exercises) to maintain ROM and muscle strength
- multidisciplinary approach: OT/PT, social work, orthopaedics, ophthalmology, rheumatology
- 1st line drug therapy: NSAIDs, intra-articular corticosteroids
- 2nd line drug therapy: DMARDs (methotrexate, sulfasalazine, leflunomide), corticosteroids (acute management of severe arthritis, systemic symptoms of JIA, topical eye drops for uveitis), biologic agents (IL-1/IL-6 inhibition for systemic arthritis, TNF antagonist for polyarticular JIA)

Limb Pain

Evaluation of Limb Pain

Table 49. Differential Diagnosis of Limb Pain

Cause	<3 yr	3-10 yr	>10 yr
Trauma	x	x	x
Infectious			
Septic arthritis	x	x	x
Osteomyelitis	x	x	x
Inflammatory			
Transient synovitis	x	x	
JIA	x	x	x
Spondyloarthritis		x	x
SLE		x	x
Dermatomyositis		x	x
HSP		x	x
Anatomic/Orthopedic			
Legg-Calvé-Perthes disease		x	x
Slipped capital femoral epiphysis			x
Osgood-Schlatter disease			x
Neoplastic			
Leukemia	x	x	x
Neuroblastoma	x	x	
Bone tumour		x	x
Hematologic			
Hemophilia (hemarthrosis)	x	x	x
Sickle cell anemia	x	x	x
Pain Syndromes			
Growing pains		x	x
Fibromyalgia		x	x
Complex regional pain syndrome			x

Must rule out infection, malignancy, and acute orthopedic conditions

History
- pattern of onset and progression of symptoms (including acuity and chronicity)
- morning stiffness, limp/weight-bearing status, night pain
- joint involvement (type, distribution) ± spine (axial) involvement
- extra-articular manifestations and systemic symptoms
- functional status: activities of daily living
- family history (arthritis, IBD, psoriasis, spondyloarthropathies, uveitis, bleeding disorders, sickle cell anemia)
- past medical illness, intercurrent infection, travel, sick contact history, joint injury

Physical Exam
- growth parameters
- screening examination (pGALS i.e. pediatric gait, arms, legs, spine exam)
- joint exam: inspection/palpation (swelling, erythema, warmth, tenderness, deformity), ROM
- adjacent structures (bone, tendon, muscle, skin)

Investigations
- basic: CBC and differential, blood smear, ESR, CRP, x-ray
- as indicated: blood (ANA, RF, culture, viral/bacterial serology, CK, PTT, sickle cell screen, immunoglobulins, complement), urinalysis, synovial fluid (cell count, Gram stain, culture), TB skin test, imaging, bone marrow aspiration, slit lamp exam

Red Flags for Limb Pain
- Fever
- Pinpoint pain/tenderness
- Pain out of proportion to degree of inflammation
- Night pain
- Weight loss
- Erythema
- Unexplained fractures

Limps

Definition
- an uneven gait pattern that is not age-appropriate; may be due to pain, weakness, or deformity
- gait can be antalgic (pain-avoidant) or non-antalgic (e.g. Trendelenberg, circumduction, equinus)

Epidemiology
- incidence of 1.8 out of 1,000 children below 14 years; M>F; R=L
- 80% of cases have associated pain

Approach
- wide differential that includes soft tissue injury, fractures, infection, inflammation, benign masses, malignant tumours, congenital deformities, growing pains, pain amplification syndromes, appendicitis, arthritis, muscular dystrophy, spinal conditions, and more
  - acute presentation: soft tissue injury (e.g. contusion), fracture, osteomyelitis, arthritis, foreign body
  - chronic presentation: rheumatic disease, dermatomyositis, rheumatic fever, IBD, SLE, congenital
  - most common diagnosis: transient synovitis
- history: comprehensive; focus on pain, physical trauma, and the presence of systemic symptoms
  - constitutional symptoms (e.g. fever, night sweats, weight loss) increase suspicion of infection, inflammation, and malignancy
  - bone malignancy: intermittent pain at rest or at night, palpable bony mass
  - red flags for a more serious condition: functional limitation, inability to weight bear, severe or localized joint pain, persistent symptoms (e.g. >7 d), change in bowel/bladder habits, or nocturnal/systemic/constitutional symptoms
  - if child abuse is suspected, contact the CAS (see *Child Abuse and Neglect, P18*)
  - physical exam: perform a distracted gait analysis and conduct palpation, power, and range of motion testing to localise the problem; compare lower limbs
  - note any bony abnormalities (e.g. scoliosis, valgus/varus limb posturing)
  - evaluate for signs of inflammation, reduced function, and referred pain
  - measure for leg-length discrepancy
  - limited internal rotation: intra-articular hip pathology (e.g. Legg-Calvé-Perthes, slipped capital femoral epiphysis)
  - limited hip abduction: developmental dysplasia
  - positive Trendelenberg test: developmental dysplasia of hip or weak hip abductors
  - flexed and externally rotated hip at rest: septic arthritis
  - children that seem generally unwell may have more serious systemic conditions (i.e. infection, inflammation, malignancy)
- investigations: not always indicated
  - if suspecting infection, inflammation, or malignancy: CBC, ESR, CRP, blood culture pre-antibiotics if infection suspected, synovial fluid analysis if septic arthritis suspected
- imaging:
  - if focal findings present: anteroposterior and lateral radiography of the identified area
  - if no focal findings: radiography of both lower limbs
  - ultrasounds are more sensitive at detecting hip effusions
  - MRI is useful for differentiating septic arthritis and transient synovitis of the hip, confirming osteomyelitis and stress fractures, and visualising malignancy
  - bone scintigraphy can be considered if other investigations do not reveal a diagnosis, but not commonly used

Lyme Arthritis

- see Infectious Diseases, ID22
- caused by *spirochete Borrelia burgdorferi*
- incidence highest among 5-10 yr
- do not treat children <8 yr with doxycycline (may cause permanent tooth discolouration)

Reactive Arthritis

- see Rheumatology, RH26
- arthritis (typically the knee) follows bacterial infection, especially with *Salmonella, Shigella, Yersinia, Campylobacter, Chlamydia,* and most commonly *Streptococcus* (post-streptococcal reactive arthritis)
- typically resolves spontaneously
- may progress to chronic illness or Reiter's syndrome (urethritis, conjunctivitis)

Septic Arthritis and Osteomyelitis

- MEDICAL EMERGENCY: prompt intravenous antibiotics, followed by 4 wk of oral antibiotics or 4-6 wk of oral antibiotics if the hip is involved
- see Orthopedic Surgery, OR11

Table 50. Microorganisms and Treatment Involved in Septic Arthritis/Osteomyelitis

Age	Pathogens	Treatment
Neonate	GBS, *S. aureus*, Gram negative bacilli	Cloxacillin + gentamicin OR cloxacillin + cefotaxime
Infant (1-3 mo)	*Kingella kingae*, *Strep*. spp., *Staph*. spp., H. influenzae type B Pathogens as per neonate	Cefazolin (IV), then cephalexin (PO) OR cloxacillin + cefotaxime OR cefuroxime
Child	*Kingella kingae* (<4 yr), *S. aureus* (>4 yr), *S. pneumoniae*, GAS	Cefazolin (IV), then cephalexin (PO)
Adolescent	As above; also *N. gonorrhoeae*	Ceftriaxone OR cefixime + azithromycin

GAS = group A *Strep*; GBS = group B *Strep*
Adapted from La Saux N, Canadian Pediatric Society, Infectious Diseases and Immunization Committee. Pediatr Child Health 2018;23(5):336-343

Systemic Lupus Erythematosus

- see Rheumatology, RH11
- autoimmune illness affecting multiple organ systems
- incidence 1 in 1000, more commonly age >10, F:M=10:1
- childhood-onset SLE vs. adult-onset SLE: children have more active disease, are more likely to have renal disease, and receive more intensive drug therapy and have a poorer prognosis compared to adults

Transient Synovitis of the Hip

Definition
- benign, self-limited inflammatory joint disorder, usually occurs after URTI, pharyngitis, AOM
- key is to differentiate from septic arthritis

Epidemiology
- 3-10 yr, M>F, more common on right side

Clinical Features
- afebrile or low-grade fever; pain typically occurs in hips or knees (referred from hip) suddenly; painful limp but full ROM (pain not as pronounced as in joint or bone infections); child does not look "toxic"
  - pain is not disabling and gradually worsens over few days, can have sudden onset of symptoms
- symptoms self-resolve over 7-10 d

Investigations
- WBC within normal limits; ESR and CRP may be mildly elevated
- joint effusions may be seen on ultrasound
  - aspirate joint and examine synovial fluid if suspicious for septic arthritis
  - MRI if suspicious for osteomyelitis or periarticular pyomyositis
- diagnosis of exclusion

Management
- goal is to manage symptoms (anti-inflammatory medications and bedrest)
  - usually resolves within 24-48 h

Complications
- Legg-Calvé-Perthes disease

Vasculitides

HENOCH-SCHÖNLEIN PURPURA

Definition
- most common childhood vasculitis, peak incidence 4-10 yr, M:F=2:1
- vasculitis of small vessels
- often have history of URTI 1-3 wk before onset of symptoms

Clinical Features
- clinical triad: 1) palpable purpura, 2) abdominal pain, 3) arthritis
- skin: palpable, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthralgia involving large joints associated with painful edema
- GI: abdominal pain, GI bleeding, intussusception
- renal: microscopic hematuria, IgA nephropathy, proteinuria, HTN, renal failure in <5%

Investigations
- no routine investigations performed – diagnosis is mainly based on clinical features
- urinalysis (blood, protein creatinine ratio), serum (urea/electrolytes, creatinine, albumin, elevated IgA)
- skin/renal biopsy – IgA deposition
- ultrasound – intussusception/perforation, testicular pain/swelling
- rule out other autoimmune conditions/vasculitides

Management
- mainly supportive (e.g. elevation for edema)
- anti-inflammatory medications for joint pain; corticosteroids for select patients
- monitor for protein on urinalysis and hypertension every month for 6 mo to check for renal disease, which may develop late (immunosuppressive therapy if severe)

Prognosis
- self-limited, resolves within 4 wk
- recurrence in about one-third of patients
- long-term prognosis dependent on severity of nephritis

KAWASAKI DISEASE

Definition
- acute vasculitis of unknown etiology (likely triggered by infection)
- medium-sized vasculitis with predilection for coronary arteries
- most common cause of acquired heart disease in children in developed countries
- peak age: 3 mo-5 yr; most common in people of East Asian or Pacific Islander descent, particularly Japanese

Kawasaki Diagnostic Criteria

Warm CREAM
Warm: >5 d fever
Conjunctival injection
Rash
Edema of hands and feet
Adenopathy
Mucosal changes

Diagnostic Criteria
- fever persisting ≥5 d AND ≥4 of the following features
  1. bilateral, non-exudative conjunctival injection
  2. oral mucous membrane changes (fissured lips, strawberry tongue, injected pharynx)
  3. changes of the peripheral extremities
     - acute phase: extremity changes including edema of hands and feet or erythema of palms or soles
     - subacute phase: periungual desquamation
  4. polymorphous rash
  5. cervical lymphadenopathy >1.5 cm in diameter (usually unilateral)
- exclusion of other diseases (e.g. scarlet fever, measles)
- incomplete Kawasaki disease: fever persisting ≥5 d and 2-3 of the above criteria
  - further evaluation dictated by CRP, ESR, and supplemental laboratory criteria

Management
- initial therapy: IVIg (2 g/kg) and low dose of ASA (3-5 mg/kg/d, max 325 mg/d)
- IVIg within 10 d of fever onset reduces risk of coronary aneurysm formation
- if fever persists 24-36 h after IVIg, repeat IVIg treatment at the same dose; if second dose fails, trial a third IVIg treatment, IV pulse methylprednisolone, or consult rheumatology for next steps
- baseline 2D-echo and follow-up periodic 2D-echo (usually at 2 and 6 wk)

Complications
- coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children, <5% if receive IVIg within 10 d of fever
- 50% of aneurysms regress within 2 yr
- anticoagulation for multiple or large coronary aneurysms

Common Medications

Table 51. Commonly Used Medications in Pediatrics

Drug Name	Dosing Schedule	Indications	Comments
acetaminophen	10-15 mg/kg/dose PO q4-6 h PRN	Analgesic, antipyretic	Not to exceed 60 mg/kg/d in neonates or 75 mg/kg/d in older children to a max of 4 g/d Causes hepatotoxicity at high doses
amoxicillin	80-90 mg/kg/d PO divided q8h	Otitis media	
dexamethasone	0.6 mg/kg PO x1 0.6 mg/kg/d PO for 2 d	Croup Acute asthma	
fluticasone (Flovent®)	Moderate dose – 250-500 µg/d divided BID High dose – >500 µg/d divided BID		
ibuprofen	5-10 mg/kg/dose PO q6-8 h	Analgesic, antipyretic	Use cautiously in patients with liver impairment, history of GI bleeding or ulcers
iron	6 mg/kg/d elemental iron PO once daily or divided TID	Anemia	Side effects: dark stool, constipation, dark urine
polyethylene glycol 3350 (PEG)	Disimpaction: 1-1.5 g/kg/d x3 d Maintenance: starting dose at 0.4-1 g/kg		
prednisone/prednisolone	1-2 mg/kg/d PO x5 d 3-4 mg/kg/d PO then taper to 1-2 mg/kg/d PO once platelet count >30 x 109/L 60 mg/m²/d PO	Asthma ITP Nephrotic syndrome	Oral prednisone is bitter tasting, consider using prednisolone
salbutamol (Ventolin®)	0.01-0.03 mL/kg/dose in 3 mL NS via nebulizer q0.5-4 h PRN 100-200 µg/dose prn, max 4-8 puffs frequency q4 h	Acute asthma Maintenance treatment for asthma	Can cause tachycardia, hypokalemia, restlessness

Source: Lau E. (2009) The 2010-2011 Formulary – The Hospital for Sick Children

Landmark Pediatric Trials

Trial Name	Reference	Clinical Trial Details
NUTRITION		
LEAP	NEJM 2015;372(9):803-813	**Title:** Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy **Purpose**: To assess the impact of peanut avoidance and consumption on the development of a peanut allergy in infants at high risk for the allergy. **Methods**: RCT consisting of 640 infants aged between 4 and 11 mo with severe eczema, egg allergy, or both. Infants were randomized to consume or avoid peanuts until the age of 60 mo. The primary outcome was the proportion of infants that developed a peanut allergy. **Results**: The infants randomized to consume peanuts resulted in a smaller proportion of children developing peanut allergies (1.9%) when compared to the group that avoided peanut consumption (13.7%). Increased levels of peanut-specific IgG4 antibody was prevalent in the consumption group. Raised titres of peanut-specific IgE antibodies were prevalent in the avoidance group. **Conclusion**: Prevalence of peanut allergy at 60 months of age was significantly reduced in the consumption group.
IMPACT	Lancet 2022;399(10322):359-371	**Title**: Efficacy and Safety of Oral Immunotherapy in Children Aged 1-3 years with Peanut Allergy (the Immune Tolerance Network IMPACT trial): A Randomised Placebo-Controlled Study **Purpose**: To determine if peanut oral immunotherapy can induce desensitisation or remission in young children with peanut allergy. **Methods**: Children (12 to 48 mo, n=146) who were reactive to ≤500 mg of peanut protein during a food challenge were randomly assigned to receive peanut oral immunotherapy or placebo for 134 weeks followed by 26 weeks of avoidance. **Results**: At week 134, 71% of children receiving peanut oral immunotherapy compared to 2% receiving placebo met the primary outcome of desensitisation (RD 69%, 95% CI 59-79; p<0.0001). After avoidance, 21% of children receiving peanut oral immunotherapy compared to 1% receiving placebo met remission criteria (RD 19%, 95% CI 10-28; p=0.0021). **Conclusion**: In children with peanut allergy, initiation of peanut oral immunotherapy before 48 mo was associated with an increase in desensitisation and remission.
DIABETES		
TODAY	NEJM 2012;366(24):2247	**Title:** A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes **Purpose**: To assess the efficacy of different treatment regimens in attaining glycemic control in youth with type 2 diabetes. **Methods**: RCT consisting of 699 patients between the ages of 10 and 17 yr with recent onset T2DM. Patients were assigned to continue metformin alone, or in conjunction with rosiglitazone, or a lifestyle modification focused on weight loss. The outcome of interest was loss of glycemic control indicated by glycated hemoglobin level of >8% for at least 6 mo. **Results**: Metformin alone resulted in a 51.7% failure rate, metformin+rosiglitazone resulted in a failure rate of 38.6%, and metformin+lifestyle intervention resulted in a failure rate of 46.6%. **Conclusion**: Metformin plus rosiglitazone was significantly better than metformin alone in achieving glycemic control within youth. Metformin plus lifestyle intervention did not have a significant impact on glycemic control when compared to metformin alone.
ELLIPSE	NEJM 2019;381(7):637	**Title:** Liraglutide in Children and Adolescents with Type 2 Diabetes **Purpose**: To assess the efficacy of liraglutide in combination with metformin as a treatment for type 2 diabetes in youth. **Methods**: RCT consisting of 134 patients between the ages of 10 and 17 yr with a BMI greater than the 85th percentile and a glycated hemoglobin level between 6.5 and 11%. Patients were randomized to receive metformin alone or metformin in combination with liraglutide. The outcome of interest was the change in glycated hemoglobin level after 26 wk of treatment. **Results**: After 26 wk, treatment with metformin alone resulted in a 0.42% increase in glycated hemoglobin levels and treatment with metformin and liraglutide in combination resulted in a 0.64% decrease in glycated hemoglobin levels. Youth taking liraglutide reported increased overall adverse events and gastrointestinal adverse events. **Conclusion**: Metformin+Liraglutide combination therapy demonstrated increased efficacy in maintaining glycemic control compared to metformin monotherapy.
RESPIRATORY SYNCYTIAL VIRUS		
MELODY	N Engl J Med. 2022;386(9):837	**Title**: Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. **Purpose**: To study the efficacy and safety of Nirsevimab, a monoclonal antibody against RSV, in late preterm and full-term babies. **Methods**: RCT consisting of 1490 infants born at gestational age of 35 wk were randomized in a 2:1 ratio to receive nirsevimab or a placebo, respectively. The outcome of interest is the presence of RSV infection within 150 d of treatment dosage. **Results**: RSV infections occurred within 1.2% of infants in the nirsevimab group and 5% of patients in the placebo group. **Conclusion**: Use of nirsevimab results in effective protection of preterm and full-term infants from RSV infection.
ASTHMA		
MANDALA	N Engl J Med 2022; 386:2071-2083	**Title**: Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma **Purpose**: To assess the efficacy of budesonide (corticosteroid) in combination with albuterol (bronchodilator) as a rescue medicine for asthmatic patients. **Methods**: RCT consisting of 3132 patients aged 4-11 yr with uncontrolled moderate to severe asthma. Patients were randomized to receive inhaled albuterol (180 µg) and budesonide (160 µg), albuterol (180 µg) and budesonide (80 µg), or 180 µg of albuterol alone for 24 wk of rescue treatment. The outcome of interest was the presence of a severe asthma exacerbation. **Results**: In the higher dose combination-treated group the risk of severe exacerbation was lowered by 26% when compared to the albuterol monotherapy. **Conclusion**: Use of albuterol in combination with budesonide as a rescue therapy reduces the risk of severe asthma exacerbation compared to albuterol monotherapy.

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Web-Based Resources

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Acronyms

ABI	ankle-brachial index	ENT	ear, nose, throat	MCP	metacarpophalangeal joint	ROM	range of motion
ABG	arterial blood gas	EOM	extraocular movement	NAC	nipple-areola complex	SGAP	superior gluteal artery perforator
AIN	anterior interosseous nerve	EPB	extensor pollicis brevis	NCS	nerve conduction studies	SIADH	syndrome of inappropriate antidiuretic hormone
APL	abductor pollicis longus	FDP	flexor digitorum profundus	NPWT	negative pressure wound therapy	SIEA	superficial inferior epigastric artery
ARDS	acute respiratory distress syndrome	FDS	flexor digitorum superficialis	NS	normal saline	SLP	speech-language pathology
ATLS	advanced trauma life support	FTSG	full thickness skin graft	OM	otitis media	SOF	superior orbital fissure
BIA-ALCL	breast implant-associated anaplastic large cell lymphoma	GAS	group A β-hemolytic Streptococcus	ORIF	open reduction and internal fixation	STSG	split thickness skin graft
BMR	basal metabolic rate	GBS	group B Streptococcus	OT	occupational therapy	TBSA	total body surface area
CK	creatine kinase	GnRH	gonadotropin-releasing hormone	PAP	profunda artery perforator	TMJ	temporomandibular joint
CMC	carpometacarpal	ICP	intracranial pressure	PIP	proximal interphalangeal joint	TUG	transverse upper gracilis
CO	carbon monoxide	IGAP	inferior gluteal artery perforator	PMN	polymorphonuclear	UCL	ulnar collateral ligament
D5W	5% dextrose in water	IP	interphalangeal	PT	physiotherapy	UV	ultraviolet
DIEP	deep inferior epigastric perforator	IVIg	intravenous immunoglobulin	PVD	peripheral vascular disease	VCA	vascularized composite allotransplantation
DIP	distal interphalangeal joint	MAP	mean arterial pressure	RA	rheumatoid arthritis		
		MC	metacarpal	RL	Ringer's lactate		

Basic Anatomy Review

Skin

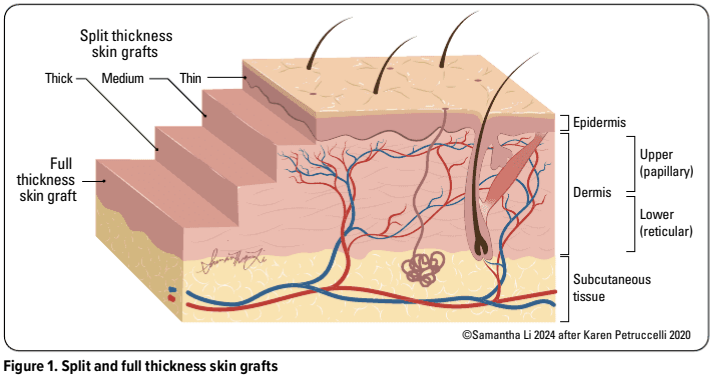

Figure 1. Split and full thickness skin grafts

Hand

Table 1. Muscles of the Forearm and Hand

Muscle	Insertion	Origin	Action
Extrinsic Flexors			
Flexor carpi ulnaris (FCU)	Pisiform and hamate	Medial epicondyle of the humerus and posterior border of the ulna	Flexion and adduction at wrist
Palmaris longus	Palmar aponeurosis	Medial epicondyle of the humerus	Flexion at wrist
Flexor carpi radialis (FCR)	Base of 2nd and 3rd metacarpal	Medial epicondyle of the humerus and anterior border of the radius	Flexion and abduction at wrist
Flexor digitorum superficialis (FDS)	Base of D2-D5 middle phalanx	Medial epicondyle of the humerus and coronoid process of the ulna	Flexion at D2-D5 PIP and MCP, and wrist
Flexor digitorum profundus (FDP)	Base of D2-D5 distal phalanx	Anterior surface of the ulna and interosseous membrane	Flexion at D2-D5 DIP, PIP, and MCP, and wrist
Flexor pollicis longus (FPL)	Base of D1 distal phalanx	Anterior surface of the radius and interosseous membrane	Flexion at D1 IP and MCP
Extensor pollicis brevis (EPB)	Base of D1 proximal phalanx	Posterior surface of the radius and interosseous membrane	Extension at D1 MCP and CMC
Abductor pollicis longus (APL)	Base of 1st metacarpal	Posterior surfaces of the ulna and radius bones, and the interosseous membrane	Abduction at D1
Extensor carpi radialis longus (ECRL)	Base of 2nd metacarpal	Lateral supracondylar ridge of the humerus	Extension and abduction at wrist
Extensor carpi radialis brevis (ECRB)	Base of 3rd metacarpal	Lateral epicondyle of the humerus	Extension and abduction at wrist
Extensor pollicis longus (EPL)	Base of 1st metacarpal	Posterior surfaces of the ulna and radius bones, and the interosseous membrane	Extension at D1 IP, MCP, and CMC
Extensor digitorum communis (EDC)	Base of D2-D5 distal and middle phalanx	Lateral epicondyle of the humerus	Extension at D2-D5 MCP, PIP, and DIP, and wrist
Extensor indicis proprius (EIP)	Base of D2 distal and middle phalanx	Posterior surface of the ulna bone and interosseous membrane	Extension at D2 MCP, PIP, and DIP, and wrist
Extensor carpi ulnaris (ECU)	Base of 5th metacarpal	Lateral epicondyle of the humerus and posterior border of the ulna bone	Extension and adduction at wrist

Table 1. Muscles of the Forearm and Hand

Muscle	Insertion	Origin	Action
Extensor digiti minimi (EDM)	Base of D5 distal and middle phalanx	Lateral epicondyle of the humerus	Extension at D5 MCP, PIP, and DIP, and wrist
Intrinsic Muscles			
Abductor pollicis brevis (APB)	Base of D1 proximal phalanx	Flexor retinaculum and tubercles of the scaphoid and trapezium bones	Abduction at D1
Opponens pollicis (OP)	Radial border of 1st metacarpal	Trapezium bone	Opposition at D1
Flexor pollicis brevis (FPB)	Base of D1 proximal phalanx	Flexor retinaculum and the tubercles of the trapezium and scaphoid bones	Flexion at D1 MCP and CMC
Adductor pollicis (ADP)	Base of D1 proximal phalanx	Capitate bone, base of the second and third metacarpal bones, and the surrounding	Adduction at D1
Lumbricals	Extensor tendons	fascia	Flexion at MCP and Extension at PIP
Palmar interossei	Extensor expansion D2-D5	Tendons of the FDP in the palm	Adduction at D2, D4, and D5
Dorsal interossei	Extensor expansion D2-D5	Metacarpal bones of the hand	Abduction at D2, D4, and D5
Abductor digiti minimi (ADM)	Base of D5 proximal phalanx	Adjacent sides of the metacarpal bones of the hand	Abduction at D5
Opponens digiti minimi (ODM)	Ulnar border of 5th metacarpal	Pisiform bone and the tendon of the FCU	Opposition of D5
Flexor digiti minimi (FDM)	Base of D5 proximal phalanx	Hook of the hamate bone and the flexor retinaculum	Flexion at D5 MCP

BONES AND NERVES

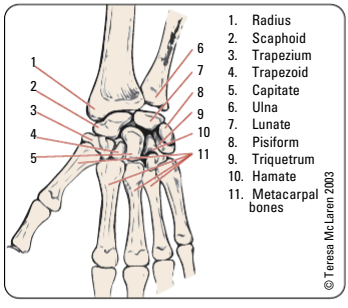

Figure 2. Carpal bones

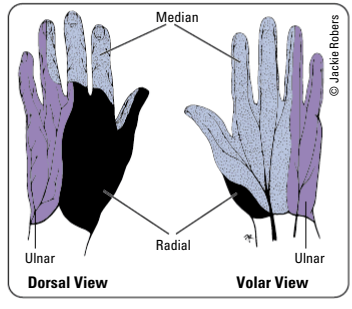

Figure 3. Sensory distribution in the hand

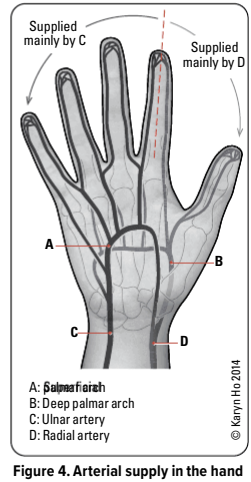

Figure 4. Arterial supply in the hand

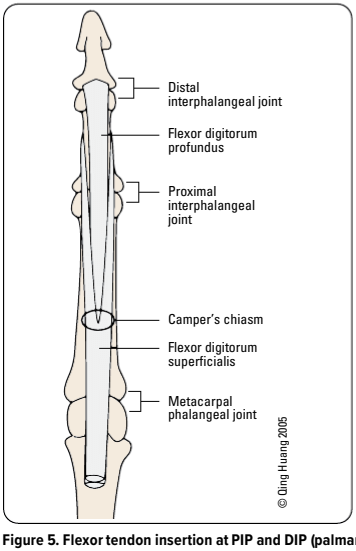

Figure 5. Flexor tendon insertion at PIP and DIP (palmar)

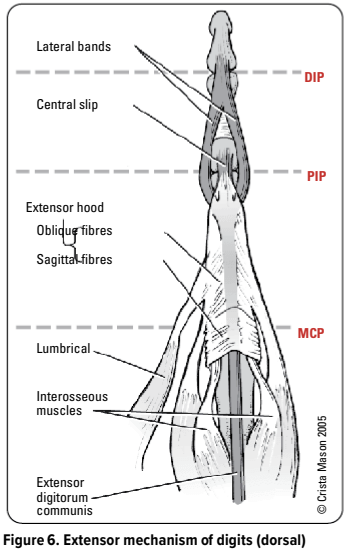

Figure 6. Extensor mechanism of digits (dorsal)

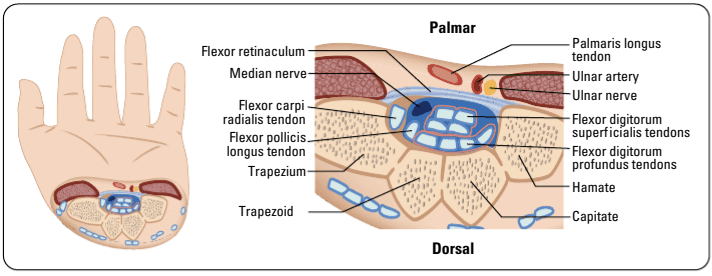

Figure 7. Carpal tunnel

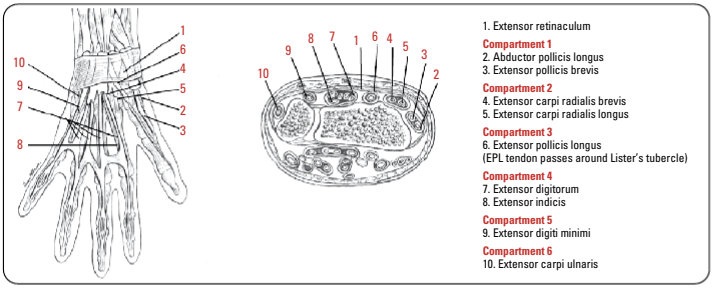

Figure 8. Extensor compartment of the wrist (dorsal view and cross-sectional view)

Brachial Plexus

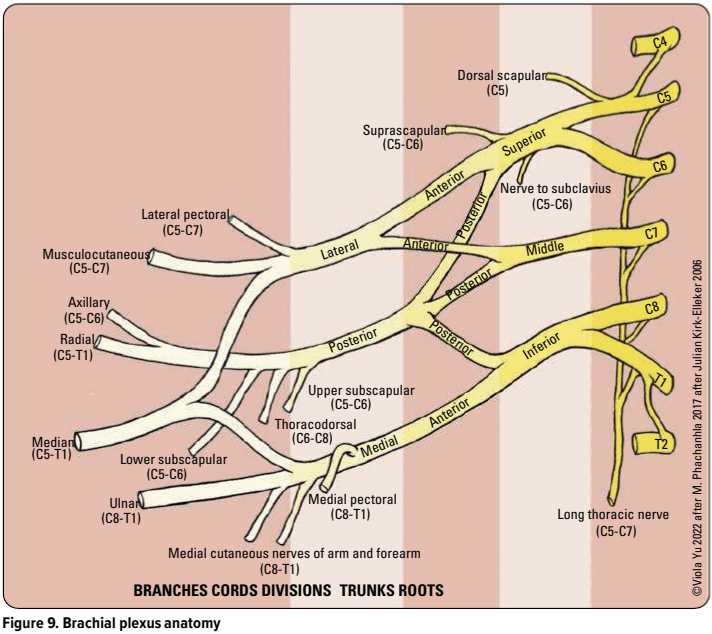

Figure 9. Brachial plexus anatomy

Carpal Tunnel
Clinical pearl: FDP crosses both DIP and PIP and FDS crosses only PIP; deeper tendons extend more distally than superficial tendons

Flexor Tendons
All require OR repair

Extensor Tendons
Emergency room repair unless proximal/ multiple tendons

Carpal Bone Mnemonic

So Long To Pinky, Here Comes The Thumb
Scaphoid
Lunate
Triquetrum
Pisiform
Hamate
Capitate
Trapezoid
Trapezium

Brachial Plexus

Rugby Teams Drink Cold Beers
Roots
Trunks
Divisions
Cords
Branches

Face

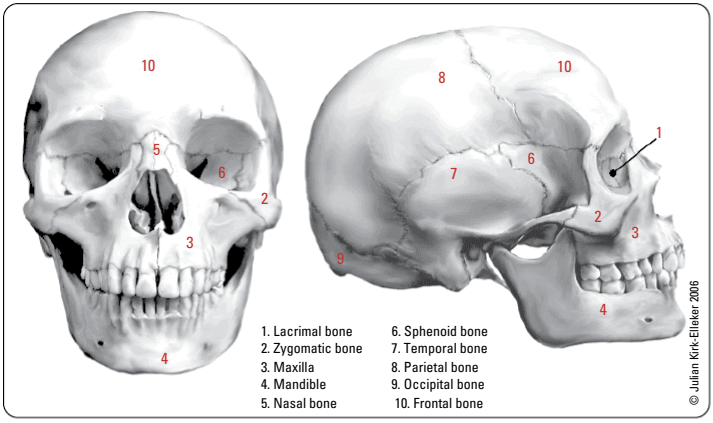

Figure 10. Skull and facial bones

Skin Lesions and Masses

Differential Diagnosis of Skin Lesions/Masses

- for background information see Dermatology, D4 and D8
- for biopsy techniques, see *Skin Biopsy Types and Techniques, PL7*

Surgical Management of Malignant Skin Lesions

- surgical treatment for all malignant skin lesions involves total excision of the primary lesion
- for pathophysiology and diagnosis see Dermatology, D40
- excision margin of lesion depends on the type of lesion and the lesion depth
- for decisions regarding reconstruction using flaps or skin grafts, see *Reconstruction, PL12*

Precursors of Malignant Lesions

Table 2. Precursors

Basal Cell Carcinoma	Squamous Cell Carcinoma	Malignant Melanoma
Nevus sebaceous of Jadassohn	Actinic keratosis	Lentigo maligna
	Bowen's disease	Giant congenital nevus
	Bowenoid papulosis	Dysplastic nevus

Surgical Margins

Table 3. Surgical Margins for Basal Cell Carcinoma

Type of Lesion	Surgical Margins
Low-Risk	3 mm
High-Risk*	3-5 mm

*High-risk features include: diameter and location (>20 mm trunk, >6 mm face, hands, and feet), poorly defined borders, recurrent lesion, poor differentiation, and type of lesion (e.g. sclerosing, morpheaform)

Table 4. Surgical Margins for Squamous Cell Carcinoma

Type of Lesion	Surgical Margins
Low-Risk	4 mm
High-Risk*	6 mm

*High-risk features include: immunosuppressed patient, depth >6 mm, ear/lip, non-sun exposed sites, poorly defined borders, recurrent lesion, poor differentiation, and histologic features (acantholytic, spindle, desmoplastic, perineural invasion)

Table 5. Surgical Margins for Malignant Melanoma

Depth of Lesion*	Surgical Margins
In situ	5-10 mm
≤1 mm	10 mm
1-2 mm	10-20 mm
2-4 mm	20 mm
>4 mm	20 mm

*Determined via excisional biopsy
0.76-1 mm thick with ulceration or mitotic rate of ≥1.0 per mm^2 , or more than 1 mm thick requires sentinel node biopsy

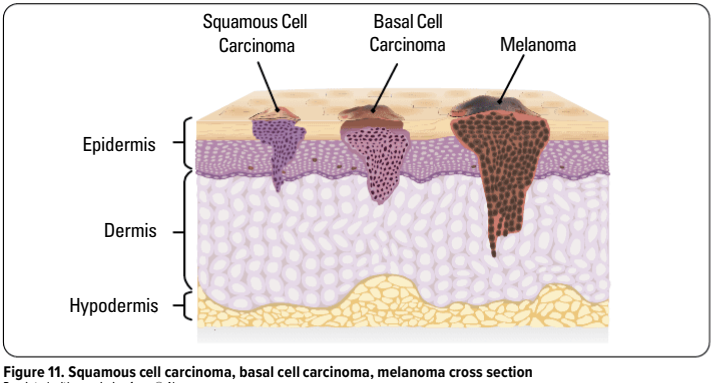

Figure 11. Squamous cell carcinoma, basal cell carcinoma, melanoma cross section
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Traumatic tattoos are permanent discolourations resulting from new skin growth over foreign material or dirt left behind in the dermis. Copious irrigation and debridement should be done as soon as possible in order to prevent traumatic tattoos, as they are very difficult to treat later

Basic Surgical Techniques

Sutures and Suturing

ANESTHESIA

- irrigate before injecting anesthetic, followed by debridement and more vigorous irrigation

Table 6. Toxic Limit and Duration of Action (1 cc of 1% solution contains 10 mg lidocaine)

	Without Epinephrine	With Epinephrine (vasoconstrictor, limits bleeding)
Lidocaine (Xylocaine®)*	5 mg/kg, lasts 45-60 min	7 mg/kg, lasts 2-6 h
Bupivicaine (Marcaine®)	2 mg/kg, lasts 2-4 h	3 mg/kg, lasts 3-7 h

* Lidocaine toxicity symptoms include: circumoral numbness, light-headedness, and drowsiness followed by tremors and seizures. Cardiac and respiratory signs are late findings

- e.g. when using 1% lidocaine without epinephrine in a 70 kg patient:
  - 1% = 1 g/100 cc = 1000 mg/100 cc = 10 mg/cc
  - toxic limit = 5 mg/kg x 70 kg = 350 mg
  - max bolus injection = 350 mg ÷ 10 mg/cc = 35 cc (may add more after 30 min)
  - combined formula: maximum allowable dose (mg/kg) x (weight in kg/10) x (1/concentration of local anesthetic (%)) = cc lidocaine.
    - e.g. with a 70 kg patient, 5 mg/kg x 70 kg/10 x 1/1 = 35 cc

IRRIGATION AND DEBRIDEMENT

- irrigate copiously with a physiologic solution such as RL or NS to remove surface clots, foreign material, and bacteria
- debride all obviously devitalized tissue; irregular or jagged wounds must be excised to produce sharp wound edges that will assist healing when approximated
- there is high-risk of infection for any wound closed primarily after 8 h

SUTURES

- use of a particular suture material is dependent on surgeon preference; however, skin should be closed with a non-absorbable, monofilament suture material when traumatic mechanisms are involved to prevent harboring bacteria in suture material

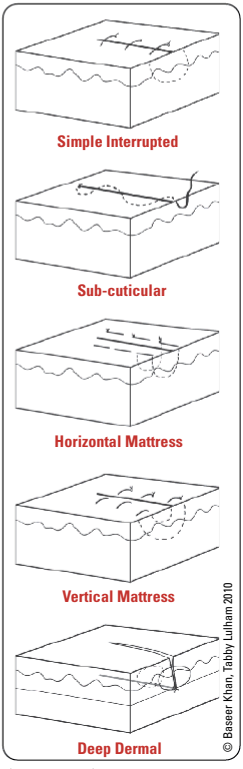

Figure 12. Basic suture methods

Table 7. Suture Materials: Absorbable vs. Non-absorbable and Monofilament vs. Multifilament

Suture Materials	Uses	Examples	Notes
Absorbable	Deep sutures under short-term tension Skin closure in children	Plain gut®, Vicryl®, Polysorb®, Biosyn®, Monocryl®, Caprosyn®, chromic gut, fast absorbing gut	Loses at least 50% of their strength in 4 wk; eventually absorbed
Non-Absorbable	Skin closure Sites of long-term tension	Nylon, polypropylene (Prolene®), stainless steel, silk, Ticron®, Ethibond®	Lower likelihood of wound dehiscence, more difficult to tie, makes track marks
Monofilament	Everyday use and optimal for contaminated and infected wounds (lower likelihood of bacterial trapping in suture material)	Monosof®, Monocryl®, Biosyn®, Prolene®	Slides through tissue with less friction; more memory/stiffness; more difficult to tie; requires multiple throws (lower knot security)
Multifilament	Used to close deep layers, such as in traumatic degloving injuries	Vicryl® and silk, Ticron®, Ethibond®	Less memory/stiffness, thus easier to work with (higher knot security); greater infection risk

Steps to Ensuring an Optimized Scar
- Incisions should be made along resting skin tension lines
- Attain close apposition of wound edges
- Minimize tension on skin by closing in layers
- Evert wound edges
- Use appropriately sized suture for skin closure (5-0 on face; 3-0, 4-0 elsewhere)
- Ensure equal width and depth of tissue on both sides
- Remove sutures within 5-7 d from the face, 10-14 d from scalp/torso/extremities

BASIC SUTURING TECHNIQUES

Basic Suture Methods
- simple interrupted: can be used in almost all situations
- subcuticular: good cosmetic result but weak, used in combination with deep sutures; not used in trauma
- vertical/horizontal mattress: for areas difficult to evert (e.g. volar hand)
- continuous over and over (e.g. "running," "baseball stitch"): time-saving, good for hemostasis
- deep/buried dermal: simple interrupted sutures placed in dermal layer, reduces skin tension for improved healing and rely on the strength of the dermis (containing collagen and elastin fibres) as opposed to the epidermis to close the wound

Other Skin Closure Materials
- tapes: (e.g. steri-strips) may be indicated for superficial wounds and those with opposable edges; tape cannot be used on actively bleeding wounds; when placed across the incision, will prevent surface marks and can be used as the primary closing material or as additional reinforcement after primary surface sutures have been removed
- skin adhesives: (e.g. 2-octyl cyanoacrylate, Dermabond®) works well on small areas without much tension or shearing; may cause irreversible tattooing
- staples: steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture); optimal in certain settings where time is a critical factor

Excision

- plan your incision along relaxed skin tension lines to minimize appearance of scar
- use elliptical incision to prevent dog ear deformity (heaped up skin at end of incision), so the length of the ellipse should be approximately 3x the width
- if needed, undermine skin edges (separate skin from underlying fascia to allow wound edge manipulation and decrease tension)
- use layered closure including deep dermal sutures (decreases tension)

Relaxed Skin Tension Lines
Natural skin/wrinkle lines with minimal linear tension. Placing incisions parallel to resting skin tension lines minimizes widening/hypertrophy and helps to camouflage scars. Relaxed skin tension lines are usually parallel to any existing wrinkle lines and perpendicular to the orientation of underlying muscle fibres (perpendicular to lines of maximum extensibility)

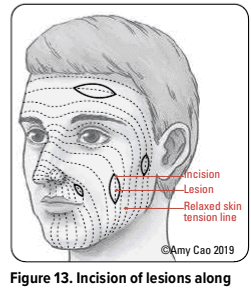

Figure 13. Incision of lesions along relaxed skin tension lines

Skin Biopsy Types and Techniques

SHAVE BIOPSY
- used for superficial lesions where sampling of the full thickness of the dermis is not necessary or practical (e.g. bridge of nose)
- most suitable lesions for shave biopsies are benign lesions either elevated above the skin or have pathology confined to the epidermis (e.g. seborrheic or actinic keratoses, skin tags, and warts)
- high-risk of recurrence with shave biopsy for any lesions, including actinic or seborrheic keratoses
- rapid, requires little training, and does not require sutures for closure (caution in patients on anticoagulant treatment)
- heals by secondary intent (moist dressings should be used)
- should not be used for pigmented lesions – an unsuspected melanoma cannot be properly staged if partially removed

NEEDLE BIOPSY
- 21 G for lymph node biopsy
- Trucut® needle biopsy for breast masses suspected for carcinoma
  - needle biopsy has fallen out of favour for lymph node biopsies; excisional biopsy is the preferred method in this circumstance

INCISIONAL BIOPSY
- can be a punch biopsy or an ellipse within the lesion (normal tissue must be included in biopsy)
- gives pathologists a portion of the lesion and the border with normal skin
- punch biopsies involve the removal of a full thickness core of tissue to allow sampling of the epidermis, dermis, fat, and potentially muscle depending on the area; performed with a round, disposable circular cutting surface on a plastic handle ranging in diameter from 2-10 mm
- punch biopsy wounds can be closed with suture or left to heal by secondary intention

EXCISIONAL BIOPSY

- performed for lesions that require complete removal for diagnostic purposes
- performed for lesions that cannot be adequately punch biopsied due to depth of lesion below surface
- for small pigmented lesions and atypical moles; if concerned about melanoma, can do a narrow margin excision for diagnosis and treatment (depending on depth in the case of melanoma)
- best for small lesions that are easily removed and primarily closed
- requires the greatest amount of expertise and time
- always requires sutures for closure

An excisional biopsy removes the entire tumour, whilst an incisional biopsy removes only a portion of the tumour. If melanoma is suspected, an excisional biopsy is preferable if possible to determine melanoma depth. Refer to Table 5 for required margins

TECHNIQUE

General

- all shave and punch biopsies performed in clinic are done using aseptic technique, but are not sterile
- sterile gloves are indicated for biopsies and excisions in all patients

Preparing the Site

- common skin antiseptics (Betadine®, chlorhexidine) can be used to prepare the biopsy site
- chlorhexidine is used in concentrations ranging from 0.5-4%. It is not typically used on the face, as it could get into the eyes or ears and may burn or cause damage. Most chlorhexidine preps also contain alcohol, which can be flammable, so allow to dry before the biopsy and certainly before using any cautery
- Betadine® (7.5% povidone–iodine) is safer for the head and neck (as to avoid the above problems with chlorhexidine) and around the eyes and ears. It is also used in "contaminated" areas such as the feet and groin
- mark the intended lesion and surgical margins with a surgical marker as the first step, since they may be temporarily obliterated following injection of the anesthetic
- for all biopsies, a sterile drape technique is indicated. Sterile towels are placed around the biopsy site after the area is cleansed and anesthetized

Anesthesia

- most commonly used local anesthetic is 1% or 2% lidocaine (with epinephrine)
- small amounts of epinephrine are added to constrict blood vessels, decrease bleeding, prolong anesthesia, and limit lidocaine toxicity. The local with epinephrine can be injected directly into the lesion
- local anesthetics with epinephrine may be used anywhere in the body, including the digits

Wounds

- wound: disruption of the normal anatomical relationships of tissue as a result of injury

Types of Wounds

- laceration: sharply cut tissue
- abrasion: superficial skin layer is removed, variable depth
- contusion: injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact, yet injured
- avulsion: skin and soft tissue forcefully separated from deeper structures, potentially compromising blood supply or resulting in full detachment (amputation)
- puncture wounds: cutaneous opening relatively small as compared with depth (e.g. needle), including bite wounds
- crush injuries: caused by compression
- burns: thermal, chemical, electrical, radiation
- ulcers: an open wound that develops on skin as a result of injury, poor circulation, or pressure

Principles of Wound Healing

Table 8. Factors Influencing Wound Healing

Local	General
Mechanical (local trauma, significant crush, avulsion, tension)	Age (affects healing rate)
Blood supply (ischemia/circulation)	Obesity/nutrition
Technique and suture materials	Tobacco smoking
Retained foreign body	Alcohol consumption
Wound infection	Chronic illness (e.g. DM, cancer, dyslipidemia, renal failure, stroke)
Collcetions (hematoma, seroma)	Immunosuppression (steroids, chemotherapy)
	Tissue irradiation
	Genetic predisposition to abnormal healing (e.g. hypertrophic or keloid scarring, collagen vascular disease)
	Skin type
	PVD
	Venous HTN

STAGES OF WOUND HEALING

- growth factors released by tissues play an important role
- scar is mature once it has completed the final stage, usually after 1-2 yr

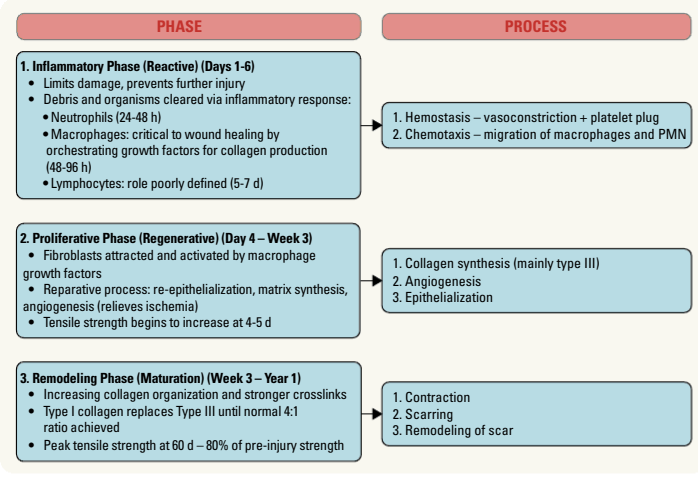
PHASE
PROCESS
1. Inflammatory Phase (Reactive) (Days 1-6)
• Limits damage, prevents further injury
• Debris and organisms cleared via inflammatory response:
• Neutrophils (24-48 h)
• Macrophages: critical to wound healing by orchestrating growth factors for collagen production (48-96 h)
• Lymphocytes: role poorly defined (5-7 d)
1. Hemostasis – vasoconstriction + platelet plug
2. Chemotaxis – migration of macrophages and PMN
2. Proliferative Phase (Regenerative) (Day 4 – Week 3)
• Fibroblasts attracted and activated by macrophage growth factors
• Reparative process: re-epithelialization, matrix synthesis, angiogenesis (relieves ischemia)
• Tensile strength begins to increase at 4-5 d
1. Collagen synthesis (mainly type III)
2. Angiogenesis
3. Epithelialization
3. Remodeling Phase (Maturation) (Week 3 – Year 1)
• Increasing collagen organization and stronger crosslinks
• Type I collagen replaces Type III until normal 4:1 ratio achieved
• Peak tensile strength at 60 d – 80% of pre-injury strength
1. Contraction
2. Scarring
3. Remodeling of scar

Figure 14. Stages of wound healing

Myofibroblasts are the cells responsible for wound contraction

TYPES OF WOUND HEALING

Primary (1°) Healing (First Intention)

- **definition**: wound closure by direct approximation of edges within hours of wound creation (e.g. with sutures, staples, skin graft, etc.)
- **indication**: recent (6-8 h, longer with facial wounds) wounds
- **contraindications**: animal/human bites, crush injuries, infection, long time lapse since injury (>6-8 h), retained foreign body

Secondary (2°) Healing/Spontaneous Healing (Second Intention)

- **definition**: wound left open to heal spontaneously (epithelialization occurs at 1 mm/d from wound margins in concentric pattern, contraction, and granulation)– maintained in inflammatory phase until wound closed; requires dressing changes
- **indication**: when 1° closure not possible or indicated (see *Primary Healing*)

Tertiary (3°) Healing/Delayed Primary Healing (Third Intention)

- **definition**: intentionally interrupt healing process (e.g. with packing, sharp debridement), then wound can be closed primarily at 4-10 d post-injury after granulation tissue has formed and there is <105 bacteria/g of tissue
- **indication**: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization, closure of fasciotomy wounds
- prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

ABNORMAL HEALING

Hypertrophic Scar

- **definition**: scar remains within boundaries of original scar
- **histology**: overabundance of dermal collagen, type III collagen oriented parallel to epidermal surface
- red, raised, widened, frequently pruritic
- **common sites**: back, shoulder, sternum
- **treatment**: scar massage, pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur)

Keloid Scar

- **definition**: scar grows outside boundaries of original scar
- **histology**: overabundance of dermal collagen, type I and III collagen in disorganized orientation
- red, raised, widened, frequently pruritic
- caused by:
  - genetic factors (highest rates in Black and Asian individuals)
  - excess tension on wound or delayed closure (as in burn wounds)

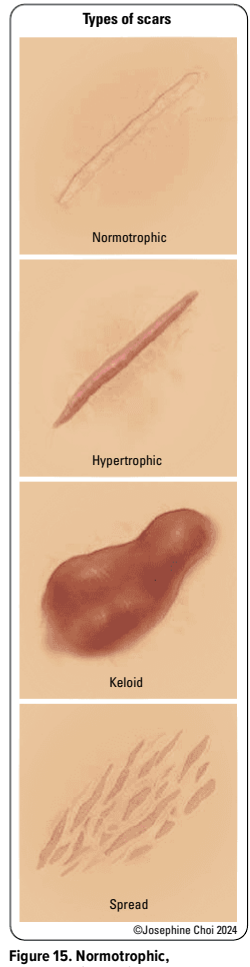

Figure 15. Normotrophic, hypertrophic, keloid, and spread scar

- **common sites**: central chest, back, shoulders, deltoid, ear, angle of mandible
- **treatment**: multimodal therapy including: pressure garments, silicone gel sheeting, corticosteroid injection, fractional carbon dioxide ablative laser, surgical excision if radiation to be performed within the next 48 h (however, this is typically very unsuccessful and there is often recurrence)

Spread Scar
- **definition**: a fine scar that gradually widens, covered by thin epithelium
- **histology**: characterized by having exactly the same order of collagen fibres as normal scars
- clinically, a typical spread scar is flat, wide, and often depressed
- common sites: abdomen, knee (e.g. dermal tearing causes abdominal striae/stretch marks post-pregnancy)
- **treatment**: surgical excision and closure

Chronic Wound
- wound fails to achieve primary wound healing within 4-6 wk
- common chronic wounds include: diabetic, pressure, and venous stasis ulcers
- **treatment**: need to address underlying cause of chronicity (e.g. infection, ischemia, metabolic conditions, immunosuppression, radiation)
- Marjolin's ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation. All chronic wounds should be biopsied to rule out Marjolin's ulcer

Infected Wounds

Definitions
- the presence of bacteria within a wound may be divided into 4 categories:
  - contamination: the presence of non-replicating microorganisms within a wound
  - colonization: the presence of replicating microorganisms within a wound
  - critical colonization: increasing bacterial burden; have delayed healing
  - infection: the presence of >105 microorganisms in a wound without intact epithelium or small amounts of a very virulent organism (e.g. GBS); have delayed healing and exhibit classic signs of infection
    - signs of infection: redness, swelling, pain, clinically unwell

Risk Factors for Infection
- Virulence of the infecting microorganism
- Amount of bacteria present
- Host resistance
- Immunocompromised host

Management of Acute Contaminated Wounds (<24 h)
- cleanse and irrigate open wound with at least 150 cc of physiologic solution (NS or RL) using sufficient pressure (4-15 PSI)
- evaluate for injury to underlying structures (vessels, nerves, tendons, and bone)
- control active bleeding, irrigation, and debridement
- debridement: removal of foreign material, devitalized tissue, and old blood (always take a swab if you suspect infection)
  - surgical debridement: blade and irrigation if indicated
- tetanus prophylaxis
- re-evaluate in 24-48 h to remove more dead tissue
  - if evidence of infection (e.g.. erythema, warmth, pain, discharge), open infected portion of wound by removing sutures, swab sample for culture and sensitivity, irrigate wound, and allow healing by secondary intention via dressing use
  - risk factors for infection include: wound >8 h, severely contaminated, immunocompromised, involvement of deeper structures (e.g. joints, fractures)
  - use systemic antibiotics if wound cultures are positive and there are signs of infection; tailor antibiotics as cultures return

Wound Exudate Characteristics

Serous drainage (plasma): thin; clear or light yellowish

Sanguineous drainage (fresh blood): bright red

Serosanguineous drainage (mix of blood and serous fluid): thin and watery; pale red to pink

Purulent drainage (infection): thick and opaque; white, yellow, or pale green

Management of Late Contaminated Wounds (>24 h)
- tetanus prophylaxis
- irrigation and debridement
- systemic antibiotics if there are clinical signs of infection
- closure: final closure via secondary intention (most common), delayed wound closure (3° closure), skin graft, or flap

Table 9. Risks for Tetanus Infection

Wound Characteristics	Tetanus-Prone	Not Tetanus-Prone
Time Since Injury	>6 h	<6 h
Depth of Injury	>1 cm	<1 cm
Mechanism of Injury	Crush, burn, gunshot, frostbite, puncture through clothing, farming injury	Sharp cut (e.g. clean knife, clean glass)
Devitalized Tissue	Present	Not present
Contamination (e.g. soil, dirt, saliva, grass)	Yes	No
Retained Foreign Body	Yes	No

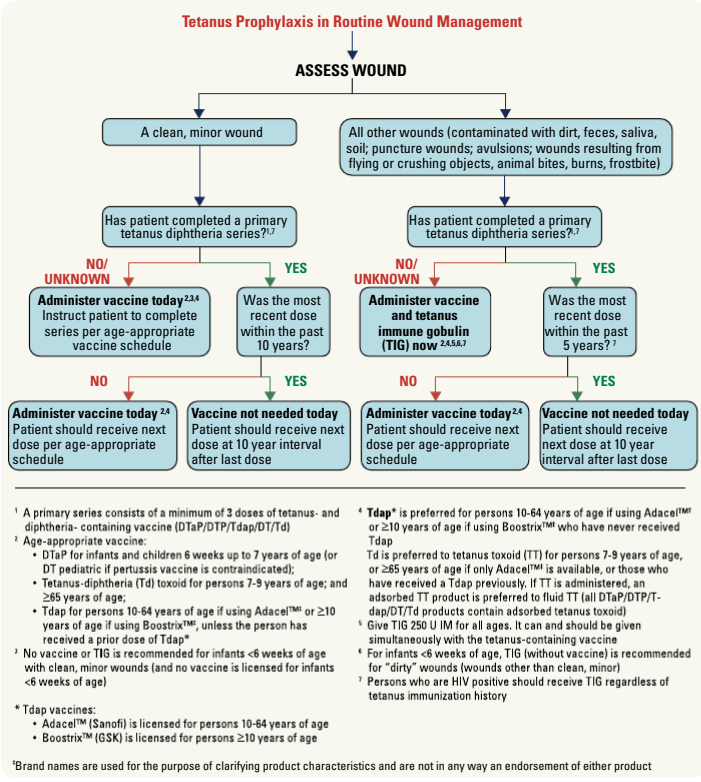
Tetanus Prophylaxis in Routine Wound Management
ASSESS WOUND
A clean, minor wound
All other wounds (contaminated with dirt, feces, saliva, soil; puncture wounds; avulsions; wounds resulting from flying or crushing objects, animal bites, burns, frostbite)
Has patient completed a primary tetanus diphtheria series?[1,7]
Has patient completed a primary tetanus diphtheria series?[1,7]
NO/ UNKNOWN
YES
NO/ UNKNOWN
YES
Administer vaccine today[2,3,4] Instruct patient to complete series per age-appropriate vaccine schedule
Was the most recent dose within the past 10 years?
Administer vaccine and tetanus immune gobulin (TIG) now[2,4,5,6,7]
Was the most recent dose within the past 5 years?[7]
NO
YES
NO
YES
Administer vaccine today[2,4] Patient should receive next dose per age-appropriate schedule
Vaccine not needed today Patient should receive next dose at 10 year interval after last dose
Administer vaccine today[2,4] Patient should receive next dose per age-appropriate schedule
Vaccine not needed today Patient should receive next dose at 10 year interval after last dose
[1] A primary series consists of a minimum of 3 doses of tetanus- and diphtheria- containing vaccine (DTaP/DTP/Tdap/DT/Td)
[2] Age-appropriate vaccine:
• DTaP for infants and children 6 weeks up to 7 years of age (or DT pediatric if pertussis vaccine is contraindicated);
• Tetanus-diphtheria (Td) toxoid for persons 7-9 years of age; and ≥65 years of age;
• Tdap for persons 10-64 years of age if using Adacel™[i] or ≥10 years of age if using Boostrix™[i], unless the person has received a prior dose of Tdap*
[3] No vaccine or TIG is recommended for infants <6 weeks of age with clean, minor wounds (and no vaccine is licensed for infants <6 weeks of age)
* Tdap vaccines:
• Adacel™ (Sanofi) is licensed for persons 10-64 years of age
• Boostrix™ (GSK) is licensed for persons ≥10 years of age
[4] Tdap* is preferred for persons 10-64 years of age if using Adacel™[i] or ≥10 years of age if using Boostrix™[i] who have never received Tdap
Td is preferred to tetanus toxoid (TT) for persons 7-9 years of age, or ≥65 years of age if only Adacel™[i] is available, or those who have received a Tdap previously. If TT is administered, an adsorbed TT product is preferred to fluid TT (all DTaP/DTP/T-dap/DT/Td products contain adsorbed tetanus toxoid)
[5] Give TIG 250 U IM for all ages. It can and should be given simultaneously with the tetanus-containing vaccine
[6] For infants <6 weeks of age, TIG (without vaccine) is recommended for "dirty" wounds (wounds other than clean, minor)
[7] Persons who are HIV positive should receive TIG regardless of tetanus immunization history
[i] Brand names are used for the purpose of clarifying product characteristics and are not in any way an endorsement of either product

Figure 16. Tetanus immunization recommendations

BITES

• see Emergency Medicine, ER47

Dog and Cat Bites

• pathogens: *Pasteurella multocida, Staphylococcus aureus, Streptococcus viridans, Moraxella* species, and *Corynebacterium* species
• **investigations**
  ▪ radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  ▪ culture for aerobic and anaerobic organisms, Gram stain
• **treatment**: Clavulin® (amoxicillin + clavulanic acid) 500 mg PO q8 h started immediately
  ▪ consider rabies prophylaxis if animal has symptoms of rabies or unknown animal
    ◆ ± rabies Ig (20 IU/kg around wound, or IM) and 1 of the 3 types of rabies vaccines (1.0 mL IM in deltoid, repeat on days 3, 7, 14, 28)
    ◆ immunoglobulin (Ig); *Definition*: A protein made by B cells and plasma cells that are present in the serum and on the surface of cells of the immune system, which act as antibodies
• irrigation with debridement
• healing by secondary intention is mainstay of treatment
• only consider primary closure for bite wounds on the face if large and done in OR; otherwise primary closure is contraindicated
• contact Public Health if animal status unknown

Human Bites

• pathogens: Staphylococcus aureus > GAS> *Eikenella corrodens* > *Bacteroides*
• serious condition, as mouth has 10 ^{9}microorganisms/mL, which can get trapped in joint space when the overlying skin forms and air-tight covering ideal for anaerobic growth (e.g. fight bite injury when fist unclenches) - can lead to septic arthritis
• **investigations**
  ▪ radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  ▪ culture for aerobic and anaerobic organisms, Gram stain

- **treatment**
  - if joint infected, urgent surgical exploration of joint, drainage, and debridement of infected tissue
  - otherwise, can be managed with I&D and antibiotic treatment in ED
  - if due to MSSA, cefazolin 2 g IV q8 h or (if penicillin allergy or MRSA) vancomycin 15 mg/kg IV q12 h + secondary closure
    - Methicillin-Sensitive *Staphylococcus aureus* (MSSA): *Definition* - MSSA is a group of gram-positive bacteria. It is commonly found on skin and is sensitive to methicillin.
    - Methicillin-resistant *Staphylococcus aureus* (MRSA): *Definition* - MRSA are genetically distinct from other strains of Staphylococcus aureus. It is responsible for several difficult-to-treat infections in humans.
  - splint

Dressings

- dressing selection depends on the wound characteristics, goal of dressing, and surgeon preference
  - as the wound progresses through healing, it will require different types of dressings; therefore, routine inspection is recommended
    - principles of dressing clean vs. infected wounds
      - clean wounds can be dressed with non-adherent dressing (which is non-adhering to epithelializing tissue); requires secondary dressing
      - infected wounds may need debridement, antibiotics, and antimicrobial dressings (i.e. iodine gauze and silver-containing dressings)
    - moist vs. dry wounds
      - purpose of dressings should be to promote moist wound healing (i.e. moistening dry wounds or drying wet wounds)
    - wide-based vs. cavitary/tunneling wounds
      - cavitary or tunneling wounds (i.e. through a fascial layer) can be packed with loose, large, and radiopaque packing materials
    - negative pressure wound therapy uses wound dressings that apply subatmospheric pressure to the wound site to promote blood flow to the region and enhance the healing process. The resultant pressure gradient promotes fluid transport from the wound bed and interstitial space to reduce wound edema
    - indications: diabetic foot ulcers, reconstructive surgery, and following debridement of acute or chronic wounds
    - contraindications: wounds with exposed vital structures (i.e. organs, blood vessels, vascular grafts) and malignant tissue

Table 10. Wound Dressings and Their Use

Dressing Type	Example	Use
Low adherent dressings	Jelonet®, tullegras, Mepilex®, Mepitel®	Flat and shallow wounds with low exudates
Semipermeable films	Mefilm®, Tegaderm Film®, Bioclusive Plus®	Wounds in difficult anatomic sites (e.g. over joints)
Hydrocolloids	CombiDERM®, Tegasorb®, Aquacel®	Hydrocolloid sheets: flat, shallow wounds with low exudate; difficult areas (elbow, heel, etc.) Hydrofibre: flat wounds, cavities, sinuses; medium – high exudate wounds
Antimicrobial	Acticoat®, Avance®, Iodosorb®	Locally infected wounds

Reconstruction

RECONSTRUCTION LADDER/ELEVATOR

Definition

- ladder: an approach to wound management with successively more complex methods of treatment where surgeons start with least complex method and progress up ladder as appropriate
- elevator: an approach to wound management where the most appropriate rather than the simplest reconstructive procedure is chosen first (i.e. we can skip steps on the ladder to achieve optimal reconstruction)

SKIN GRAFTS

Definition

- tissue composed of epidermis and varying degrees of dermis, that does not carry its own blood supply. Survival requires the generation of new blood vessels from the recipient site bed

Donor Site Selection

- must consider size, hair pattern, texture, thickness of skin, and colour (facial grafts best if taken from "blush zones" - harvest sites above clavicle where colour match for full thickness grafts is optimized (e.g. pre/post auricular or neck))
- partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)

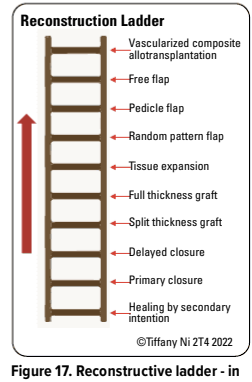

Figure 17. Reconstructive ladder - in order of increasing complexity

Partial Thickness Skin Graft Survival

- initial stabilization of graft provided by fibrin network between recipient site and graft
- 3 phases of skin graft "take"
  1. plasmatic imbibition: diffusion of nutrition from recipient site (first 48 h)
  2. inosculation: growth of vessels from bed and graft toward each other (d 2-3)
  3. neovascular ingrowth: growth of new vessels which vascularize graft (d 3-5)
- requirements for graft survival
  - well-vascularized bed (recipient site). Examples of unsuitable beds include heavily irradiated wounds and infected wounds
  - coagulation begins as soon as graft is placed on bed
  - good contact between graft and recipient bed. Staples, sutures, splinting, and pressure dressings are used to prevent movement/shearing of graft and hematoma or seroma formation
  - low bacterial count at recipient site ($<105/cm^3$, to prevent infection)
- common reasons for graft loss: hematoma/seroma, infection, mechanical force (e.g. shearing, pressure), radiotherapy

Classification of Skin Grafts

1. by species
   - autograft: from same individual
   - allograft (homograft): from same species, different individual
   - xenograft (heterograft): from different species (e.g. porcine)
2. by thickness: see *Table 11*

Table 11. Skin Grafts

	Split Thickness Skin Graft	Full Thickness Skin Graft
Definition	Epidermis and part of dermis	Epidermis and all of dermis
Donor Site	More sites	Donor sites limited by the ability to use primary closure
Healing of Donor Site	Re-epithelialization via dermal appendages in wound edges	Primary closure
Re-Harvesting	~10 d (faster on scalp)	N/A
Graft Take	More reliable and better survival; shorter nutrient diffusion distance	Lower rate of survival (thicker, slower revascularization)
Contraction*	Less 1° contraction, greater 2° contraction (less with thicker graft)	Greater 1° contraction, less 2° contraction
Aesthetic	Poor	Good
Advantages	Takes well in less favourable conditions	Resists contraction, better colour match
	Can cover a larger area	May use on face and fingers
	Can be meshed for greater area	
	Allows for extravasation of blood/serum	
	Large number of donor sites	
Disadvantages	Contracts significantly, abnormal pigmentation, high susceptibility to trauma, donor site scar, requires well vascularized bed	Requires well vascularized bed
Uses	Large areas of skin, granulating tissue beds	Face (colour match), site where thick skin or decreased contracture is desired (e.g. finger)

*1° contraction: immediate reduction in size upon harvesting; 2° contraction: reduction in size once graft placed on wound bed and healing has occurred

Meshed Grafts

- split thickness grafts can be meshed after harvest by a mesher to a variety of ratios
- **advantages**
  - prevents accumulation of fluids (e.g. hematoma, seroma)
  - covers a larger area
  - best for contaminated recipient site
- **disadvantages**
  - poor cosmesis ("alligator hide" appearance)
  - has greater secondary contraction than full thickness grafts (see *Table 11*)

OTHER GRAFTS

Table 12. Various Tissue Grafts

Graft Type	Use	Preferred Donor Site
Bone (Vascularized or Non-Vascularized)	Repair rigid defects	Cranial, rib, iliac, fibula, scapula
Cartilage	Restore contour of ear and nose	Ear, nasal septum, costal cartilage
Tendon	Repair or replace a damaged tendon	Palmaris longus, plantaris (present in 85% of population)
Nerve	Conduit for regeneration across nerve gap	Sural, antebrachial cutaneous, medial brachial cutaneous
Vessel	Bridge vascular gaps	Forearm or foot vessels for small vessels, saphenous vein for larger vessels; veins are typically used for any vessel graft
Dermis	Contour restoration (± fat for bulk); not used often	Groin, abdomen, thigh
Fat	Contour restoration	Abdomen, thighs, buttocks

FLAPS

- **definition**: tissue of varying composition (muscle alone, skin and subcutaneous tissue, bone alone with vascular supply, etc.), that has a known blood supply (random, pedicled, or named); not dependent on neovascularization, unlike a graft
- may consist of: skin, subcutaneous tissue, fascia, muscle, tendon, bone, other tissue (e.g. omentum)
- **classification**: based on tissue composition, blood supply to skin (random, axial), location of the donor site (local, regional, distant), etc.
- **indications for flaps**
  - replaces tissue loss due to trauma or surgery (reconstruction)
  - provides skin and soft tissue coverage through which surgery can be carried out later
- **complications**: flap loss due to hematoma, seroma, infection, poor flap design, extrinsic compression (dressing too tight) or vascular failure/thrombosis, fat necrosis (in free and pedicled flaps)

Random Pattern Flaps

- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply
- flap choice is often a combination of available tissue, type of tissue needed, location of reconstruction site with respect to donor site, blood supply, ability to close the donor site, and surgeon preference
- **types**
  - **rotation**: semicircular tissue rotated around a pivot point for defect closure; commonly used on sacral pressure sores, scalp, and cheek defects (height of triangular defect:radius of flap curve should be 0.5-1:1)
  - **transposition**: tissue is transposed (e.g. lifted up from its native location and brought into the defect) around a pivot point from one location to another; commonly used on certain areas of the face using adjacent areas of excess skin laxity
  - **Z-plasty**: two triangular flaps are designed around a scar to reorient a scar, lengthen the line of a scar, or to break up a scar
  - **advancement flaps (V-Y, Y-V):** defect is closed with unidirectional tissue advancement
    - **single/bipedicle V-Y flaps**: wounds with lax surrounding tissue; the pedicle flap is attached to the donor site via a pedicle containing the blood supply

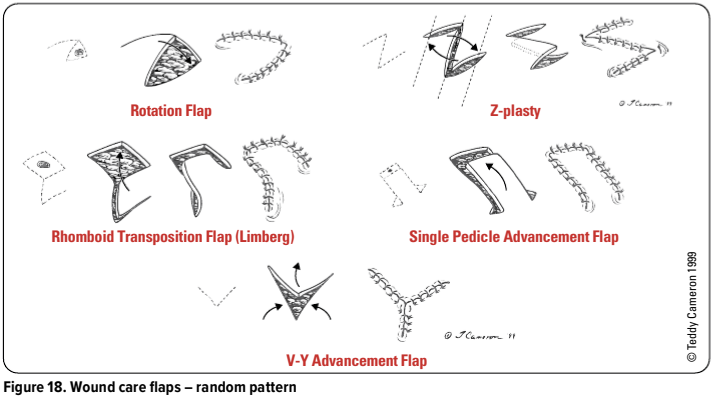

Figure 18. Wound care flaps – random pattern

Axial Pattern Flaps (Arterialized)
- flap contains a well-defined artery and vein
- allows greater length:width ratio (5-6:1)
- types
  - **peninsular flap**: skin and vessel intact in pedicle
  - **island flap**: vessel remains intact, but is skeletonized such that the pedicle is better defined
  - **free flap**: segment of tissue with named blood supply (artery and vein) that can be harvested with that blood supply and re-anastomosed in a different anatomical location by microsurgical techniques
- can be sub-classified according to categories such as tissue type, blood supply type, and calibre of vessels
  - e.g. myogenic, myocutaneous, fasciocutaneous

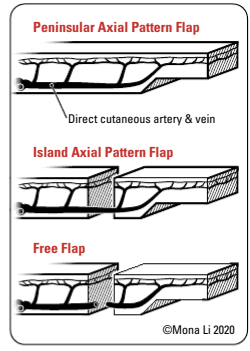

Figure 19. Axial/arterial pattern flaps

Free Flaps
- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and vein to a flap, and performing a microsurgical anastomosis between these and the vessels in the recipient wound
- types: muscle and skin (common), bone, jejunum, omentum, fascia, or any combination of tissue where a common blood supply can be harvested to provide vascular supply to all the tissue types
- e.g. radial forearm, scapular, latissimus dorsi

Table 13. Characteristics of Healthy Free Flap

Characteristic	Normal	Arterial Insufficiency	Venous Insufficiency
Colour*	Pink	Pale	Purple or blue
Temperature	Warm	Cool	Warm or cool
Arterial Pulse (Doppler)	+	–	±
Turgor	Soft, but with some firmness	Decreased tissue firmness	Increased (tissue firmness with tissue stiffness)
Capillary Refill	2-5 s	>5 s	<2 s

*Variation depending on patient's skin colour

Vascularized Composite Allotransplantation (i.e. composite tissue allotransplantation)
- considered free flaps because it is a functional and vascularized construct; vessels are anastomosed, as well as the nerves
- similar to solid organ transplantation, although VCA involves the transplantation of a composite of tissue (skin, fat, muscle, nerve, and vessels) from one individual to another, after matching sex and blood ± HLA type (e.g. face, limb, penile, uterine transplants)
- skin is highly immunogenic, containing effector T cells and antigen presenting cells which can mount a proinflammatory state and contribute to allograft rejection; regulatory T cells (Tregs) can modulate effector T cell inflammation through inhibitory cytokines (e.g. TGF-β, IL-10)
- patients require immunosuppression therapy
  - induced with antithymocyte globulin and basiliximab (anti-T cell antibodies)
  - maintained with tacrolimus, mycophenolate mofetil, and prednisone
- acute rejection appears to affect the skin first; treatment consists of increased oral or IV steroids, mono/polyclonal antibodies, and topical immunosuppressants

Soft Tissue Infections

Erysipelas

Definition
- acute skin infection of the upper dermis and superficial lymphatics (more superficial than cellulitis)

Eiology
- typically caused by GAS

Clinical Features
- intense erythema, induration, and sharply demarcated borders (differentiates it from other skin infections)

Treatment
- penicillin or first-generation cephalosporin (e.g. cefazolin or cephalexin)

Cellulitis

Definition
- non-suppurative infection of skin and subcutaneous tissues

Etiology
- skin flora are most common organisms: *Staphylococcus aureus*, GAS
- immunocompromised: Gram-negative rods and fungi

Clinical Features
- source of infection
  - trauma, recent surgery
  - PVD, DM – xerotic skin in feet/toes
  - foreign bodies (IV, orthopedic pins)
- systemic symptoms (fever, chills, malaise)
- pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (common in GAS; visible red streaking in skin proximal to area of cellulitis)

Investigations
- CBC, blood cultures
- culture a collection/aspirate from wound if open wound

Treatment
- antibiotics: first line – cephalexin 500 mg PO q6 h or cloxacillin 500 mg PO q6 h x 7 d; if complicated (e.g. lymphangitis, DM, severe infection, oral antibiotic therapy failure), consider IV cefazolin 1-2 g q8 h or IV cloxacillin, IV penicillin. All patients should have reassessment in 48 h for resolution if on an oral antibiotic
- outline area of erythema to monitor success of treatment
- immobilize upper and lower extremities; consider non-weight bearing for lower extremities

Necrotizing Fasciitis

Definition
- rapidly spreading, very painful infection of the fascia with necrosis of surrounding tissues
- some bacteria create gas that can be felt as crepitus and can be seen on x-rays (subcutaneous emphysema)
- infection spreads rapidly along deep fascial plane and is limb- and life-threatening; this is a surgical emergency

Etiology
- Type I: polymicrobial (more common in immunocompromised)
- Type II: monomicrobial, usually GAS (more common in healthy patients)

Risk Factors
- immunocompromised, DM, obesity, IV drug use, age >50 yr, PVD, and malnutrition

Clinical Features
- disproportionate pain to clinical findings and beyond border of erythema
- overlying dermatologic findings including blistering, ecchymoses, edema ± crepitus (subcutaneous gas from anaerobes)
- patients may look deceptively well at first, but have some disorganized physiology on initial labs and may rapidly become very sick (e.g. nausea, fever, diarrhea, dizziness, malaise)
- late findings:
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of bullae
  - cutaneous gangrene, subcutaneous emphysema

Investigations
- a clinical diagnosis
- CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, gas collection, myonecrosis, and possible source of infection)
- severely elevated CK: usually means myonecrosis (late sign)
- bedside incision, exploration, and incisional biopsy when ruling out conditions, clinical feature is not supportive, or difficult exam
- during incisional biopsy, often see "dishwater pus" (GAS) and a hemostat easily passed along fascial plane (fascial biopsy to rule out in equivocal situations)

Treatment
- vigorous resuscitation (ABCs)
- urgent surgical debridement: remove all necrotic tissue, copious irrigation with plans for repeat surgery in 24-48 h
- IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4 h and clindamycin 900 mg IV q6 h until final cultures available (the combination can be synergistic if GAS) or vancomycin and clindamycin
- postoperative ICU admission and infectious disease consult after urgent surgical debridement by plastic surgery

Ulcers

Lower Limb Ulcers

Traumatic Ulcers (Acute)

- failure of wound to heal, usually due to compromised blood supply and unstable scar, secondary to pressure or bacterial colonization/infection
- usually over bony prominence ± edema ± pigmentation changes ± pain
- treatment, in consultation with vascular surgery
  - any debridement of ulcer and compromised tissues must be preceded by ABIs and vascular Doppler
  - ulcers or compromised tissues left to heal by secondary intention with dressings may need reconstruction with local or distant flap in select cases; vascular status of limb must be assessed clinically and via vascular studies (i.e. ABI, duplex Doppler)

Table 14. Venous vs. Arterial vs. Diabetic Ulcers

Characteristic	Venous (70% of vascular ulcers)	Arterial	Diabetic
Cause	Valvular incompetence Venous HTN	2° to small and/or large vessel disease (be aware of risk factors)	Peripheral neuropathy: decreased sensation Atherosclerosis: microvascular disease
History	Dependent edema, trauma Rapid onset ± thrombophlebitis, varicosities	Arteriosclerosis, claudication Usually >45 yr Slow progression	DM Peripheral neuropathy Trauma/pressure
Common Distribution	Medial malleolus ("Gaiter" locations)	Distal locations (e.g. lower limb, feet)	Pressure point distribution (more likely metatarsal heads)
Appearance	Yellow exudates Granulation tissue Varicose veins Brown discolouration of surrounding skin	Pale/white, necrotic base ± dry eschar covering	Necrotic base
Wound Margins	Irregular	Even ("punched out")	Irregular or "punched out" or deep
Depth	Superficial	Deep	Superficial/deep
Surrounding Skin	Venous stasis discolouration (brown)	Thin, shiny, dry skin; hairless, cool	Thin, dry skin ± hyperkeratotic border Hypersensitive/ischemic
Pulses	Normal distal pulses	Decreased or no distal pulses	Decreased pulses likely (take caution in calcified vessels)
Vascular Exam	ABI >0.9 Doppler; abnormal venous system	ABI <0.9 Pallor on elevation, rubor on dependency Delayed venous filling	ABI is inaccurately high (due to PVD) Usually associated with arterial disease (microvascular/ macrovascular disease)
Pain	Moderately painful Increased with leg dependency, decreased with elevation No rest pain	Extremely painful Decreased with dependency, increased with leg elevation and exercise (claudication) Rest pain	Painless (if neuropathy) No claudication or rest pain Associated paresthesia, anesthesia
Treatment	Rest, leg elevation Compression at 30 mmHg (stockings or elastic bandages) (Ensure ABI is safe for compression) Moist wound dressings ± topical, systemic antibiotics if infected ± wound dressings	Rest, no elevation, no compression Moist wound dressing ± topical and/or systemic antibiotics if infected Modify risk factors (smoking, diet, exercise, etc.) Vascular surgical consultation (angioplasty or bypass) Treat underlying conditions (DM, proximal arterial occlusion, etc.)	Control DM Careful wound care Foot care Orthotics, off-loading Early intervention for infections (topical and/or systemic antibiotics if infected) Vascular surgical consultation

In patients with DM, ABI can be falsely normal due to incompressible arteries secondary to plaques/calcification

Pressure Ulcers

Common Sites

- over bony prominences; 95% on lower body

Stages of Development

1. hyperemia: disappears 1 h after pressure removed
2. ischemia: follows 2-6 h of pressure
3. necrosis: follows >6 h of pressure
4. ulcer: necrotic area breaks down

Classification (National Pressure Ulcer Advisory Panel 2014)

- Stage I: non-blanchable erythema present >1 h after pressure relief, skin intact
- Stage II: partial-thickness skin loss
- Stage III: full-thickness skin loss into subcutaneous tissue

- Stage IV: full-thickness skin loss into muscle, bone, tendon, or joint
  - if an eschar is present, must fully debride before staging possible
- Stage X: unstageable

Prevention
- clean and dry skin, frequently reposition, special beds or pressure relief surface, proper nutrition, activity, early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, immunocompromised, DM, etc.), treatment of underlying medical conditions

Treatment
- treatment plan individualized to patient
- **4 main principles:**
  - preventative measures such as pressure relief, assessing for pressure points (e.g. in wheelchairs), managing continence issues, diverting contaminants (e.g. urine and feces), and ensuring appropriate nutrition
  - treatment of underlying medical issues
  - moisture reduction
  - wound bed preparation and treatment
- systemic antibiotics for infections
- assess for possible reconstruction

Complications
- cellulitis, osteomyelitis, sepsis, gangrene

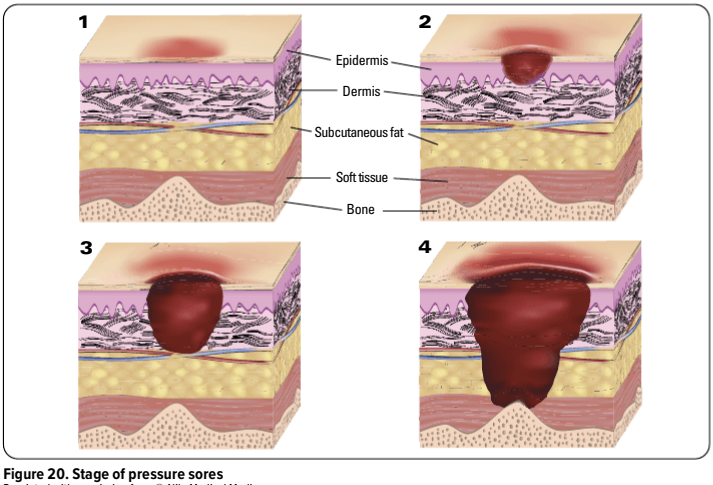

Figure 20. Stage of pressure sores
Reprinted with permission from © Alila Medical Media

A Nutritional Formula Enriched with Arginine, Zinc, and Antioxidants for the Healing of Pressure Ulcers: A Randomized Trial
Ann Intern Med 2015;162(3):167-174
Purpose: To determine whether supplementation with arginine, zinc, and antioxidants within a high-calorie, high-protein formula improves pressure ulcer healing.
Methods: 200 adult patients from long-term care and home care services with stage II, III, and IV pressure ulcers received either an energy-dense, protein-rich oral formula enriched with arginine, zinc, and antioxidants or an equal volume of an isocaloric, isonitrogenous formula for 8 wk.
Results: Supplementation with the enriched formula resulted in a greater reduction in pressure ulcer area. A more frequent reduction in area of 40% or greater at 8 wk was also seen.
Conclusion: Among malnourished patients with pressure ulcers, 8 wk of supplementation with an oral nutritional formula enriched with arginine, zinc, and antioxidants improves pressure ulcer healing.

Burns

Burn Injuries

Causal Conditions
- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

Most Common Etiologies
- children: scald burns
- adults: flame burns

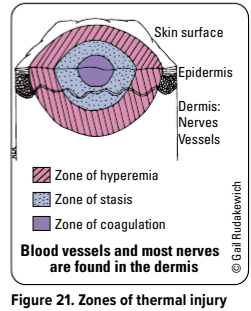

Figure 21. Zones of thermal injury

Table 15. Skin Function and Burn Injury

Skin Function	Consequence of Burn Injury	Intervention Required
Thermoregulation	Prone to lose body heat	Must keep patient covered and warm
Control of Fluid Loss	Loss of large amounts of water and protein from the skin and other body tissues	Adequate fluid resuscitation is imperative
Mechanical Barrier to Bacterial Invasion and Immunological Organ	High-risk of infection	Antimicrobial dressings (systemic antibiotics if signs of specific infection present) Tetanus prophylaxis if not already administered

Pathophysiology of Burn Wounds

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent
- zone of hyperemia: vasodilation from inflammation; entirely viable, cells recover within 7 d; contributes to systemic consequences seen with major burns
- zone of stasis (edema): decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24-48 h without proper treatment
  - factors favouring cell survival: moist, aseptic environment, rich blood supply
  - zone where appropriate early intervention has most profound effect in minimizing injury
- zone of coagulation (ischemia): no blood flow to tissue → irreversible cell damage → cellular death/necrosis

Diagnosis and Prognosis

- burn size
  - % of TBSA burned: rule of 9s for 2° and 3° burns only (children <10 yr use Lund-Browder chart)
  - for patchy burns, surface area covered by patient's palm (fingers adducted) represents approximately 1% of TBSA
- age: more complications if <3 yr or >60 yr
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see *Table 16, PL20*)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see *Indications for Transfer to Burn Centre, PL20*)
- inhalation injury: can severely compromise respiratory system, affect fluid requirement estimation (underestimate), mortality secondary to ARDS
- associated injuries (e.g. fractures)
- comorbid factors can exacerbate extent of injury (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure, other trauma)

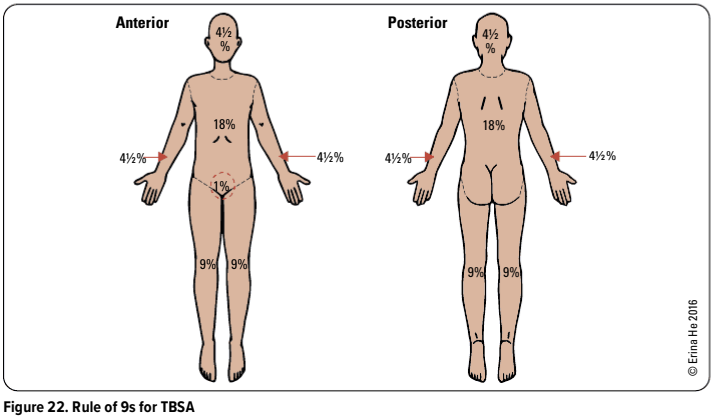

Figure 22. Rule of 9s for TBSA

Prognosis best determined by burn size (TBSA), age of patient, presence/absence of inhalation injury

Circumferential burns can restrict respiratory excursion and/or blood flow to extremities and require escharotomy

TBSA does not include areas with 1° burns

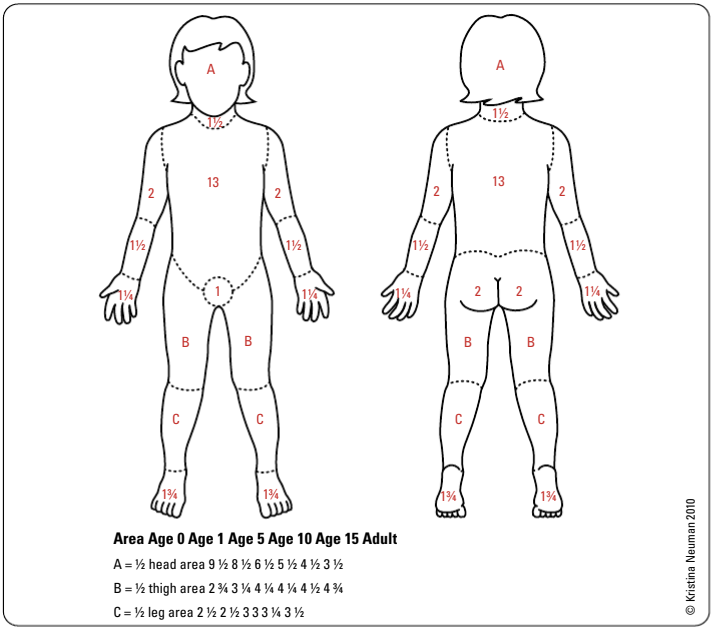

Figure 23. Lund-Browder diagram

Table 16. Burn Depth (1st, 2nd, 3rd degree)

Nomenclature	Traditional Nomenclature	Depth	Clinical Features
Erythema/Superficial	First degree	Epidermis	Painful, sensation intact, erythema, blanchable
Superficial-Partial Thickness	Second degree	Into superficial (papillary) dermis	Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present
Deep-Partial Thickness	Second degree	Into deep (reticular) dermis	Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn
Full Thickness	Third degree	Through epidermis and dermis	Injury to underlying tissue structures (e.g. muscle, bone) Insensate (nerve endings destroyed), hard leathery eschar that is black, grey, white, or cherry red in colour; hairs do not stay attached, may see thrombosed veins
	Fourth degree	Injury to underlying tissue structures (e.g. muscle, bone)	

Indications for Transfer to Burn Centre

American Burn Association Criteria

- patients with partial or full-thickness burns that involve the hands, feet, genitalia, face, eyes, ears, and/or major joints or perineum
- electrical burns including lightning (internal injury underestimated by TBSA) and chemical burns
- inhalation injury (high risk of mortality and may lead to respiratory distress)
- burn injuries in patients with medical comorbidities which could complicate management and recovery
- any patients with simultaneous trauma and burns should be stabilized for trauma first, then triaged appropriately to burn centre
- any patients with burn injury who will require special emotional, social, and rehabilitation intervention
- children with burns in a hospital not equipped with pediatric care specialists

Acute Care of Burn Patients

- adhere to ATLS protocol
- resuscitation using Parkland formula to estimate fluid loss secondary to injury and cardiac output and initiate treatment (see *Table 17*)
- extra fluid administration required if:
  - burn >80% TBSA
  - 4° burns
  - associated traumatic injury
  - electrical burn
  - inhalation injury
  - delayed start of resuscitation
  - pediatric burns
- monitor resuscitation
  - urine output is best measure: maintain at >0.5 cc/kg/h (adults) and 1.0 cc/kg/h in children <12 yr
  - maintain a clear sensorium, HR <120/min, MAP >70 mmHg
- burn-specific care
  - escharotomy in circumferential extremity burns, including digits
  - prevent and/or treat burn shock: 2 large bore IVs for fluid resuscitation
  - insert Foley catheter to monitor urine output
  - identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
  - determine TBSA affected first, since depth is difficult to determine initially (easier to determine after 24 h)
- tetanus prophylaxis if needed
  - all patients with burns >10% TBSA or deeper than superficial-partial thickness, need 0.5 cc tetanus toxoid
  - also give 250 U of tetanus Ig if prior immunization is absent/unclear or the last booster >10 yr ago
- baseline laboratory studies (Hb, U/A, BUN, CXR, electrolytes, Cr, glucose, CK, ECG, cross-match if traumatic injury, ABG, carboxyhemoglobin)
- cleanse, debride, and treat the burn injury (antimicrobial dressings)
- early excision and grafting are standard of care and important for outcome

Respiratory Problems

- 3 major causes
  - burn eschar encircling chest
    - distress may be apparent immediately
    - perform escharotomy to relieve constriction
  - CO poisoning
    - may present immediately or later
    - treat with 100% O_2 by facemask (decreases half-life of carboxyhemoglobin from 210 to 59 min) until carboxyhemoglobin <10%
  - smoke inhalation leading to pulmonary injury
    - chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
    - risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
    - watch for secondary bronchopneumonia (3-25 d) leading to progressive pulmonary insufficiency
    - intubate patient with any signs of inhalation injuries

Burn Wound Healing

Table 17. Burn Shock Resuscitation (Parkland Formula)

Parkland Formula	
Hour 0-24	4 cc x mass in kg x % TBSA with 1/2 of total in first 8 h from time of injury and 1/2 of total in next 16 h from time of injury
Hour 24-30	0.35-0.5 cc plasma x mass in kg x % TBSA
>Hour 30	D5W at rate to maintain normal serum sodium

* Remember to add maintenance fluid to resuscitation

Inhalation Injuries 101

Indicators of Inhalation Injury

- Injury in a closed space
- Facial burn
- Singed nasal hair/eyebrows
- Soot around nares/oral cavity
- Hoarseness
- Conjunctivitis
- Tachypnea
- Carbon particles in sputum
- Elevated blood CO levels (i.e. brighter red)
- Suspected inhalation injury requires immediate intubation due to impending airway edema; failure to diagnose inhalation injury can result in airway swelling and obstruction, which, if untreated, can lead to death
- Neither CXR or ABG can be used to rule out inhalation injury
- Direct bronchoscopy now used for diagnosis
- Signs of CO poisoning (headache, confusion, coma, arrhythmias)

Table 18. Burn Wound Healing

Depth	Healing
First Degree	No scarring; complete healing
Second Degree (superficial partial)	Spontaneously re-epithelialize in 7-14 d from retained epidermal structures
	± Residual skin discolouration
	Hypertrophic scarring uncommon; grafting rarely required
Deep Second Degree (deep partial)	Re-epithelialize in 14-35 d from retained epidermal structures
	Hypertrophic scarring frequent
	Grafting recommended to expedite healing
Third Degree (full thickness)	Re-epithelialize from the wound edge
	Grafting/flap necessary to replace dermal integrity and limit hypertrophic scarring
Fourth Degree	Often results in amputations
	If not requiring amputation, needs flap for coverage after debridement (does not re-epithelialize, cannot graft)

Treatment

- three stages
  1. assessment: depth determined
  2. management: specific to depth of burn and associated injuries
  3. rehabilitation
- first degree
  - treatment aimed at comfort
  - topical creams (pain control, keep skin moist) ± aloe
  - oral NSAIDs (pain control)
- superficial second degree/partial thickness
  - daily dressing changes with topical antimicrobials (such as Polysporin®); leave blisters intact unless impaired or over joint and inhibiting motion
- deep second degree/deep partial thickness and third degree/full thickness
  - prevent infection and sepsis (significant complication and cause of death in patients with burns)
    - most common organisms: *S. aureus, P. aeruginosa*, and *C. albicans*
      - d 1-3 (rare): Gram-positive
      - d 3-5: Gram-negative (*Proteus, Klebsiella*)
    - topical antimicrobials: treat colonized wounds (from skin flora, gut flora, or caregiver)
  - remove dead tissue
- surgically debride necrotic tissue, excise to viable (bleeding) tissue

Table 19. Antimicrobial Dressings for Burns

Antibiotic	Pain with Application	Penetration	Adverse Effects
Silver Nitrate (0.5% solution)	None	Minimal	May cause methemoglobinemia, stains (black), leeches sodium from wounds
Nanocrystalline Silver-Coated Dressing (Acticoat®)	None or transient	Medium, does not penetrate eschar	May stain, producing a pseudoeschar or facial discolouration (bluish-gray discolouration; raised liver enzymes
Silver Sulfadiazine (cream) (Flamazine®, Silvadene®)	Minimal	Medium, penetrates eschar	Slowed healing, leukopenia, mild inhibition of epithelialization; pseudoeschar must be washed off prior to each application
Sulfamylon®	Moderate	Well, penetrates eschar; only used on ears	Mild inhibition of epithelialization, may cause metabolic acidosis with wide application

- early excision and grafting is the mainstay of treatment for deep/full thickness burns
- initial dressing should decrease bacterial proliferation

Other Considerations in Burn Management

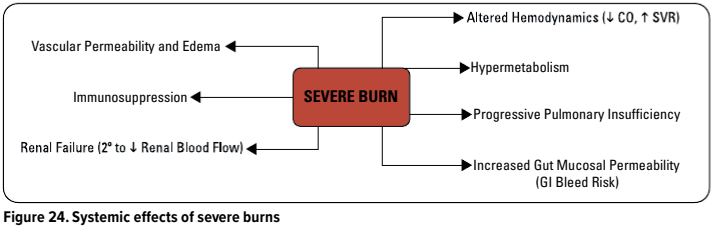
Altered Hemodynamics (↓ CO, ↑ SVR)
Vascular Permeability and Edema
Hypermetabolism
Immunosuppression
SEVERE BURN
Progressive Pulmonary Insufficiency
Renal Failure (2° to ↓ Renal Blood Flow)
Increased Gut Mucosal Permeability (GI Bleed Risk)

Figure 24. Systemic effects of severe burns

- nutrition
  - hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
  - consider nutritional supplementation (e.g. calories, vitamin C, vitamin A, Ca^{2+}, Zn^{2+}, Fe^{2+})

Risk Factors for Infection of Burn Wounds

Patient Related

Extent >30% TBSA

- Depth: full thickness and deep partial thickness
- Patient age (higher risk with very young and very old)
- Comorbidities
- Wound dryness
- Wound temperature
- Secondary impairment of blood flow to wound
- Acidosis

Microbial Factors

- Density >105 organisms per gram of tissue
- Motility
- Virulence and metabolic products (endotoxin, exotoxin, permeability factors, other factors)
- Antimicrobial resistance

Topical Silicone Gel versus Placebo in Promoting the Maturation of Burn Scars: a Randomized Controlled Trial

Plast Reconstr Surg 2010; 126(2):524-531.

Purpose: To determine the effectiveness of topical silicone gel in promoting burn scar maturation.

Methods: Forty-six scars were randomized to management with silicone gel or placebo.

Results: Silicone gel-treated scars were significantly less rough and itchy at 3 mo.

Conclusions: Topical silicone gel significantly improves the texture and pruritus of burn scars.

- immunosuppression and sepsis
  - must keep bacterial count <105 bacteria/g of tissue (blood culture may not be positive)
  - signs of sepsis: sudden onset of hyper/hypothermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 h post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
- GI bleed may occur with burns >40% TBSA (usually subclinical)
  - treatment: tube feeding or NPO if there is a GI bleed, antacids, H2 blockers (preventative)
- renal failure secondary to under resuscitation, drugs, myoglobin, etc.
- progressive pulmonary insufficiency
  - can occur after: smoke inhalation, pneumonia, cardiac decompensation, sepsis
- wound contracture and hypertrophic scarring
  - outcomes optimized with timely wound closure, splinting, pressure garments, and physiotherapy

Special Considerations

CHEMICAL

- major categories: acid burns, alkaline burns, phosphorus burns, chemical injection injuries
- common agents: cement, hydrofluoric acid, phenol, tar
- mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
  - acids → coagulation necrosis
  - alkalines → saponification followed by liquefactive necrosis
- severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
- burns are deeper than they initially appear and may progress with time

Treatment (General)

- ABCs, monitoring
- remove contaminated clothing and brush off any dry powders before irrigation
- irrigation with water for 1-2 h under low pressure (contraindicated in elemental metal burns, such as sodium, potassium, magnesium, and lithium; in these cases, soak in mineral oil instead)
- inspect eyes; if affected, wash with saline and refer to ophthalmology
- inspect nails, hair, and webspaces
- correct metabolic abnormalities and provide tetanus prophylaxis if necessary
- contact poison control line if necessary
- local wound care 12 h after initial dilution (debridement)
- wound closure same as for thermal burn
- beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

Table 20. Special Burns and Treatments

Burns	Treatment
Acid Burn	Water irrigation, followed by dilute solution of sodium bicarbonate
Hydrofluoric Acid	Water irrigation; clip fingernails to avoid acid trapping; topical calcium gel ± subcutaneous injection of calcium gluconate ± 10% calcium gluconate IV depending on amount of exposure and pain
Sulfuric Acid	Treat with soap/lime prior to irrigation as direct water exposure produces extreme heat
Tar	Remove with repeated application of petroleum-based antibiotic ointments (e.g. Polysporin®)

ELECTRICAL BURNS

- injury occurs due to flow of current through body, arc flash, or clothing catching on fire
- depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
- often presents as small punctate burns on skin, with extensive deep tissue damage which requires debridement
- electrical burns require ongoing monitoring (ECG and neurovascular status), as latent injuries can occur
- watch for system-specific damages and abnormalities
  - abdominal: intraperitoneal damage
  - bone: fractures and dislocations especially of the spine and shoulder
  - cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
  - muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
  - neurological: seizures and spinal cord damage
  - ophthalmology: cataract formation (late complication)
  - renal: acute tubular necrosis resulting from toxic levels of myoglobin and hemoglobin
  - vascular: vessel thrombosis → tissue necrosis (increased Cr, K^+, and acidity), decrease in RBC count (beware of hemorrhages/delayed vessel rupture)

Treatment
- ABCs, primary and secondary survey, treat associated injuries onotnh
- beware of cardiac arrhythmias (continue cardiac monitoring)
- monitor: hemochromogenuria (myoglobin/hemoglobin in urine), compartment syndrome, urine output
- wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
- debride nonviable tissue early and repeat PRN (every 48 h) to prevent sepsis
- amputations frequently required

FROSTBITE
- see Emergency Medicine, ER46

Hand

Traumatic Hand

Table 21. Key Features of the History and Physical Exam of the Injured Hand

HISTORY		
Key Questions	Age	Tetanus status
	Hand dominance	Diabetes
	Occupation	Smoking status
	Time and place of accident	Last oral intake
	Mechanism of injury	Previous history of hand injury
	Initial treatment received	
PHYSICAL EXAM		
	Structure	**Examination**
Observation	Position of finger	Abnormal cascade (fingers normally slightly flexed and point towards scaphoid), scissoring
	Deformity	Bony protrusions or specific deformities (e.g. mallet, boutonnière, and swan neck deformity)
	Bruising or swelling	May indicate underlying skeletal injury
	Sweating pattern (usually felt more so than from observation)	May indicate denervation
	Anatomical structures beneath	If open laceration, need to explore within wound (under sterile conditions)
Vascular Status	Radial and ulnar arteries	Palpate pulses Allen's test
	Digital arteries	Assess capillary refill (<2-3 s) Doppler ultrasound
	Temperature and skin turgor	For each test, need to compare both sides
Sensory (see *Figure 3, PL3*)	Median nerve	Volar radial tip of index finger
	Ulnar nerve	Volar ulnar tip of little finger
	Radial nerve	Dorsal web space of the thumb
	Digital nerves	2-point discrimination on both the radial and ulnar side of the DIP creases (static or moving 2-point discrimination)
Motor Function	Median nerve	Flex DIP of index finger (to test the AIN branch)
		Touch the tip of the index finger to the thumb trying to break through ("OK sign") (to test the AIN branch)
		Thumb to ceiling with palm up (to test the recurrent motor branch)
		Thumb to tip of 5th digit (to test the recurrent motor branch)
	Ulnar nerve	Extrinsic muscles: flex DIP of little finger
		Intrinsic muscles: abduct index finger ("Peace sign") or patient able to hold piece of paper between adducted thumb and index finger and resist pulling ("Froment's sign")
	Radial nerve	Extrinsic muscles: extend thumb ("thumb's up") and wrist
Range of Motion	Tendons, bones, joints, nerves	Assess active and passive range of motion of wrist: extension/flexion/ulnar/radial deviation; finger abduction/adduction/flexion/extension; thumb flexion/extension/abduction/adduction/opposition
Tendons	FDP	Stabilize PIP in extension, ask patient to flex fingers (at DIP)
	FDS	Stabilize non-exam fingers in extension (neutralizes FDP) and ask patient to flex examination finger (at PIP)
Palpation	Bones	Focal tenderness or abnormal alignment
	Joints	Instability may indicate ligamentous injury or dislocation

Compartment Syndrome
Watch out for these signs: tense, painful extremity (worse on passive stretch), paresthesia/paralysis, pallor, and distal pulselessness (often late in process). Intracompartmental pressures can be measured, commonly via needle manometry (generally abnormal pressures are considered to be >30-40 mmHg). Of note, upper and lower extremity pressures are different and comorbidities can result in variability in measured pressures. As such, indication for an emergent fasciotomy is based on clinical diagnosis; if untreated, end result is ischemic contracture of the extremity (Volkmann's contracture)

Approach to Hand Lacerations

TIN AX
Tetanus prophylaxis
Irrigate with **NS** (copious irrigation and debridement in a timely manner)
NPO (NPO if you are considering replanting or an urgent OR, otherwise most operations are done as elective procedures)
Antibiotic prophylaxis (controversial – most require no antibiotics, mainly needed for lacerations associated with fractures)
X-rays

Allen's Test: You need to exsanguinate the hand by having the patient open and close the hand. Then, while patient's hand is firmly closed, occlude both radial and ulnar arteries. Once fist is open, release one artery and assess collateral flow. The process should be repeated for the other artery

Tissue Resistance to Electrical Current
Nerve < vessel/blood < muscle < skin < tendon < fat < bone

General Management of Hand Injuries (Categorized by Tissue)

Nerves
- test the nerve function BEFORE putting in local anesthesia
- primary repair for a clean injury within 2 wk and without concurrent major injuries; secondary repair if >2 wk (may require nerve graft)
- epineurial repair of all digital nerves with minimal tension
- postoperative: dress wound, elevate hand, and immobilize
- Tinel's sign (cutaneous percussion over the repaired nerve) produces paresthesias and defines level of nerve regeneration
  - Wallerian degeneration occurs in the first 2 wk, which is why there is no Tinel's sign until after this time period
  - a peripheral nerve regenerates at 1 mm/d
  - paresthesias felt at area of percussion because regrowth of myelin (Schwann cells) is slower than axonal regrowth → percussion on exposed free-end of axon generates paresthesia

Hand Exam

Never blindly clamp a bleeding vessel as nerves are often found in close association with vessels

Never explore any volar hand wound in the ED

Arterial bleeding from a volar digital laceration is likely associated with a nerve laceration (nerves in digits are superficial to arteries)

Vessels
- often associated with nerve injury in the digits (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 h
- close skin, then dress, immobilize, and splint hand with fingertips visible
- monitor colour, capillary refill, skin turgor, fingertip temperature post-revascularization

Tendons
- most tendon lacerations require repair
- most extensors are repaired in the emergency room, flexors are repaired in the operating room within 2 wk
- see *Tendons, PL27*

Bones
- see *Fractures and Dislocations, PL28*

Nailbed
- subungual hematomas >50% of the nail surface area need to be drained (trephination), done under a digital block by puncturing nail plate
- if suspecting greater severity of injury (e.g. distal phalanx displaced fracture, laceration of nail bed), remove nail plate to examine underlying nailbed under digital block anesthesia
- irrigate wound and nail thoroughly
- suture repair of nailbed with chromic suture
- replace cleaned nail, which acts as a splint for any underlying distal phalangeal fracture and prevents adhesion formation between nail fold and nailbed

Hand Infections

Principles
- trauma is most common cause
- 90% caused by Gram-positive organisms
- most common organisms (in order): *S. aureus, S. viridans, GAS, S. epidermidis*, and *Bacteroides melaninogenicus* (MRSA is becoming more common)

TYPES OF INFECTIONS

Deep Space Infections
- abscess formation in deep spaces of the hand, Parona's space, web spaces, or most commonly thenar or midpalmar space

Felon
- **definition**: abscess in the pulp of a fingertip or thumb that occurs following a puncture wound into the pad of the digit; may be associated with osteomyelitis
- **treatment**: elevation, warm soaks, cloxacillin 500 mg PO q6 h (if in early stage); if obvious abscess or pressure on the overlying skin or failure to resolve with conservative measures, then I&D, take cultures/Gram stain, and adjust antibiotics to culture results

Flexor Tendon Sheath Infection

- *Staphylococcus* > *Streptococcus* > Gram-negative rods
- **definition**: abscess within the flexor tendon sheath (flexor tenosynovitis), commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated
- **clinical features**: Kanavel's 4 cardinal signs
  1. point tenderness along flexor tendon sheath from A-1 pulley onwards
  2. severe pain on passive extension of digit
  3. fusiform swelling of entire digit
  4. flexed posture (increased comfort)
- **treatment**
  - non-suppurative: antibiotics, resting hand splint, and elevation until infection resolves, hand therapy after
  - suppurative (produces pus): I&D in OR

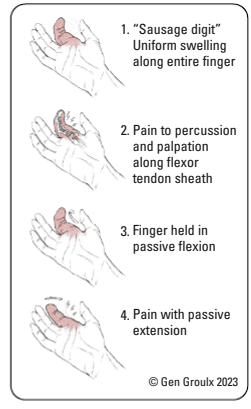
1. "Sausage digit" Uniform swelling along entire finger
2. Pain to percussion and palpation along flexor tendon sheath
3. Finger held in passive flexion
4. Pain with passive extension
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Figure 25. Kanavel's cardinal Signss

Herpetic Whitlow

- HSV-1, HSV-2
- definition: painful vesicle(s) around fingertip or thumb
  - often found in medical/dental personnel and children
- clinical features: can be associated with fever, malaise, and lymphadenopathy, prodromal phase
  - patient is infectious until lesion has completely healed
- treatment: diagnosed clinically, if in doubt confirm with viral culture/PCR or Tzanck smear, usually self-limited, consider oral acyclovir in severe cases; debridement of these lesions is contraindicated

Paronychia

- acute = *Staphylococcus*; chronic = *Candida*
- **definition**: infection (granulation tissue) of soft tissue around fingernail (within the paronychium and/or beneath eponychial fold)
- **etiology**
  - acute paronychia: a "hangnail," artificial nails, and nail biting
  - chronic paronychia: prolonged exposure to moisture
- **treatment**
  - acute paronychia: warm compresses and oral antibiotics if caught early; if abscess present, drainage with blade (avoid hitting nail bed) and oral/IV antibiotics; if abscess extends to below nail plate, nail plate removal may be required
  - chronic paronychia: antifungals, eponychial marsupialization; nail plate removal may be required

Amputations

Hand or Finger

- emergency management: injured patient and amputated part requires attention
  - patient: x-rays (stump and amputated part), NPO, clean wound and irrigate with NS, dress stump with non-adherent dressing, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/erythromycin)
  - **amputated part**: x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice
- indications for replantation
  - **age**: children often better results than adults
  - **level of injury**: thumb and multiple digit amputations are higher priority; multiple level amputation is a contraindication to replant
  - **nature of injury**: clean cut injuries have greater success; avulsion and crush injuries are relative contraindications to replant
- if replant contraindicated, manage stump with revision amputation
  - involves debriding stump of wound, trimming back the bone and nerve endings, and gently closing the skin
  - commonly done in the ED under digital block

Tendons

Common Extensor Tendon Deformities

Table 22. Extensor Tendon Deformities

Injury	Definition	Zone	Etiology/Clinical Features	Treatment
Mallet Finger	DIP flexed with loss of active extension	1	There are bony and non-bony mallets Bony: fracture of distal phalanx distal to tendon insertion Non-bony: forced flexion of the extended DIP leading to extensor tendon rupture at DIP (e.g. sudden blow to tip of the finger)	Splint DIP in extension for 6 wk, followed by 2 wk of night splinting; if inadequate improvement after 6 wk, check splinting routine and recommend 4 more wk of continuous splinting
Boutonnière Deformity	PIP flexed, DIP hyperextended	3	Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx Associated with RA or trauma (laceration, volar dislocation, acute forceful flexion of PIP)	Splint PIP in extension and allow active DIP motion
Swan Neck Deformity	PIP hyperextended, DIP flexed	1, 3	Trauma (PIP volar plate injury) Associated with RA and old, untreated mallet deformity Splint to prevent PIP hyperextension or DIP flexion	Corrective procedures involve tendon rebalancing or arthrodesis/arthroplasty

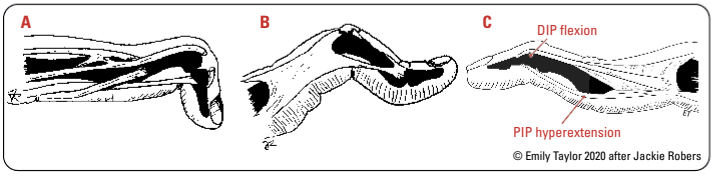

Figure 26. Extensor tendon deformities: (A) Mallet finger deformity (B) Boutonnière deformity (C) Swan neck deformity

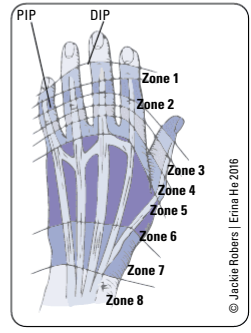

Figure 27. Zone of extensor tendon injury (odd numbered zones fall over a joint)

De Quervain's Tenosynovitis

- **definition**: tenosynovitis is inflammation of the tendon and/or its sheath. Most common is De Quervain's tenosynovitis (inflammation of the extensor tendons in the 1st dorsal compartment (APL and EPB))
- **clinical features**
  - positive Finkelstein's test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)
  - pain localized to the 1st extensor compartment
  - tenderness and crepitation over radial styloid may be present
  - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)
- **treatment**
  - mild: NSAIDs, splinting, and steroid injection into the tendon sheath
  - severe: surgery to open 1st dorsal compartment and release stenotic tendon sheaths of APL and EPB

Ganglion Cyst

- **definition**
  - fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin
  - most common soft tissue tumour of hand and wrist (60% of masses)
- **clinical features**
  - most commonly on the dorsal wrist overlying the scapholunate ligament, followed by the volar surface of the wrist overlying the radioscaphoid or scaphotrapezial joints
  - 3 times more common in women than in men
  - more common in younger individuals (2nd to 4th decades)
  - can be large or small (may drain internally so size may wax and wane)
  - often non-tender, although tenderness increased when cyst is smaller (from increased pressure within smaller cyst sac)
- **treatment**
  - conservative treatment: observation and reassurance; advise patient against rupturing cyst
  - aspiration (recurrence rate 30-60% within one yr, risk of damaging nearby neurovascular structures)
  - steroid injection if painful (done in combination with aspiration, as results alone are no better than aspiration)
  - consider operative excision of cyst and stalk (recurrence rate 5.9% for dorsal wrist ganglion, 30% for volar)

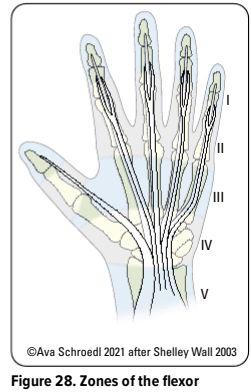

Figure 28. Zones of the flexor tendons

A-2 and A-4 pulleys are most important for function; prevent bowstringing of tendons

Common Flexor Tendon Deformities
- flexor tendon zones (important for prognosis of tendon lacerations)
- "no-man's land" (zone 2)
  - between distal palmar crease and mid-middle phalanx
  - zone where superficialis and profundus lie ensheathed together
  - recovery of glide very difficult after injury

Stenosing Tenosynovitis (Trigger Finger/Thumb)
- definition: inflammation and thickening of tendon or tendon sheath/pulley (most commonly at A-1 pulley near MCP), preventing smooth gliding of tendon through the sheath/pulley and resulting in locking of thumb or finger in flexion/extension
- etiology: idiopathic or associated with RA, DM, hypothyroidism, gout, and pregnancy
- clinical features
  - ring finger is most commonly affected, then long finger and thumb
  - patient complains of catching, snapping, or locking of affected finger
  - tenderness to palpation/nodule at palmar aspect of MCP over A-1 pulley
  - women are 4 times more likely to be affected than men
- non-surgical treatment
  - NSAIDs
  - steroid injection; injections less likely to be successful in patients >60 yr, or symptoms greater than 6 mo
  - splint
- surgical treatment
  - indicated if no relief of symptoms or minimal relief with steroids
  - incise A-1 flexor pulley to permit unrestricted, full active finger motion

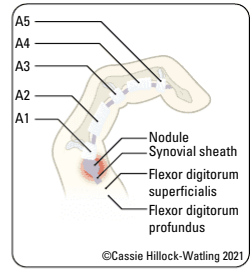

Figure 29. Digital flexor pulley system

Fractures and Dislocations

- for fracture principles, see Orthopedic Surgery, OR5

FRACTURES
- about 90% of hand fractures are stable in flexion (splint to prevent extension)
- **position of safety**
  - wrist extension 0-30°
  - MCP flexion 70-90°
  - IP full extension
  - this is done if you want to immobilize a fracture but are not sure whether there are other injuries
- stiffness secondary to immobilization is the most important complication

Distal Phalanx Fractures
- most commonly fractured bone in the hand
- usual mechanism is crush injury and thus accompanied by soft tissue injury
- subungual hematoma is common and must be decompressed, especially if there is involvement of >50% of the nail surface area, see *General Management of Hand Injuries (Categorized by Tissue), PL25*
- treatment: 3 wk of digital splinting (immobilize the DIP with a STAX™ splint); if intra-articular fracture displaced >30%, then percutaneous pinning (K-wires) and splint, or ORIF

Proximal and Middle Phalanx Fractures
- check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit
- non-displaced or minimally displaced: closed reduction (if extra-articular), buddy tape to neighbouring stable digit, elevate hand, careful motion of extremity with splint to prevent reinjury, splinted for 2-3 wk
- displaced, non-reducible, not stable with closed reduction, or rotational or scissoring deformity: percutaneous pinning (K-wires) or ORIF, and splint

Metacarpal Fractures
- generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
- **Boxer's fracture**: acute angulation of the neck of the 5th metacarpal into palm
  - mechanism: blow on the distal-dorsal aspect of closed fist
  - loss of prominence of metacarpal head, volar displacement of head
  - up to 30-40° angulation may be acceptable
  - closed reduction should be considered to decrease the angle
  - if stable, ulnar gutter splint for 4-6 wk
- **Bennett's fracture**: two-piece fracture/dislocation of the base of the thumb metacarpal, usually intra-articular
  - unstable fracture
  - APL pulls MC shaft proximally and radially, causing adduction of thumb
  - treat with percutaneous pinning or ORIF, followed by thumb spica for 6 wk
- **Rolando fracture**: T- or Y-shaped fracture of the base of the thumb metacarpal
  - treated like a Bennett's fracture

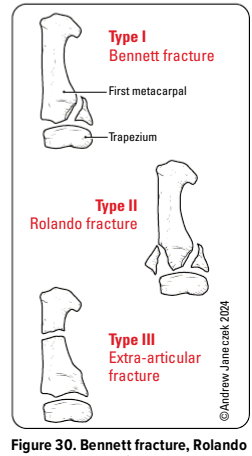

Figure 30. Bennett fracture, Rolando fracture, extra-articular fracture

DISLOCATIONS
- treatment: must be reduced as soon as possible
- dislocation vs. subluxation
  - dislocation: severe injury where articular surfaces of a joint are no longer in contact with one another
  - subluxation: articular surfaces of a joint are partially out of place (i.e. "partial dislocation" – often unstable and requires reduction)

PIP and DIP Dislocations (PIP more common than DIP)
- usually dorsal dislocation (commonly from hyperextension)
- 3 views of hand needed with x-ray imaging to assess degree of dislocation (posteroanterior, oblique, and lateral)
- if closed dislocation: closed reduction and splinting in position of function for 1 wk or buddy taping, and early mobilization (prolonged immobilization causes stiffness)
- open injuries are treated with wound care, irrigation, and debridement, followed by closed or open reduction and antibiotics

MCP Dislocations (relatively rare)
- dorsal dislocations much more common than volar dislocations
- dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
- two types of dorsal dislocation
  - simple (reducible with manipulation): treat with closed reduction and splinting for 2-4 wk at 60-70° MCP flexion
  - complex (irreducible, most commonly due to volar plate blocking the reduction): treat with open reduction

UCL Injury of the Hand
- forced abduction of thumb (e.g. ski pole injury)
- skier's thumb: acute UCL injury; if stable (elbow valgus stress test), treated with splint for 6-8 wk; if unstable, patient may have Stener lesion
- Gamekeeper's thumb: chronic UCL injury, often requires open repair and tendon graft for stabilization
- Stener lesion: the distal portion of the UCL can detach and flip superficial to the adductor aponeurosis and will not appropriately heal; requires open repair (requires x-ray imaging to diagnose)
- evaluation: radially deviate thumb MCP joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion

Dupuytren's Disease

Definition
- proliferative disorder of the palmar fascia, forming nodules (usually painless), fibrous cords, and flexion contractures at the MCP and interphalangeal joints
- flexor tendons not involved
- Dupuytren's diathesis: male sex, early age of onset, strong family history (autosomal dominant inheritance), involvement of multiple digits, bilateral involvement, and involvement of sites other than palmar aspect of hand, including the plantar fascia (Ledderhose's) and the penis (*Peyronie's*; see Urology, Table, U33)

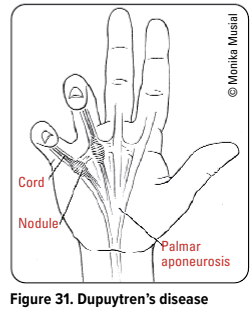

Figure 31. Dupuytren's disease

Epidemiology
- unusual in Asian patients or patients of African descent, high incidence in northern European patients, men > women, often presents in 5th-7th decade of life; associated with but not caused by alcohol use, smoking, and DM

Clinical Features
- nodules, cords, and contractures of MCP, PIP, and DIP
- order of digit involvement (most common to least common): ring > little > long > thumb > index
- risk of recurrence

Treatment
- palmar pit or nodule: no surgery (steroid injections for pain)
- palpable band/cord with no limitation of extension (i.e. no contracture) of either MCP or PIP: no surgery
- MCP contracture >30° or PIP contracture of any degree: needle aponeurotomy, collagenase *Clostridium histolyticum* (Xiaflex®) injection (indicated if cord is palpable), or surgical fasciectomy
- contractures impeding function and/or hygiene: needle aponeurotomy, collagenase injection, or surgical fasciectomy
- MCP joints have better outcomes than PIP joints post-treatment (achievement of near full extension, lower risk of recurrence)

Carpal Tunnel Syndrome

Definition
- median nerve compression at the level of the flexor retinaculum/transverse carpal ligament

Etiology
- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumours, hypertrophic synovial tissue, fracture callus, and osteophytes); metabolic and physiological (pregnancy, hypothyroidism, acromegaly, and RA); job/hobby-related repetitive trauma, especially forced wrist flexion

Epidemiology
- F:M=4:1, most common entrapment neuropathy

Clinical Features
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/rubbing
- on exam, sensory loss in median nerve distribution (see *Figure 3, PL3*), but thenar eminence sensory loss is spared (palmar cutaneous branch given off prior to carpal tunnel)
- decreased light touch and 2-point discrimination at DIP radial and ulnar creases; discriminative touch often lost first
- advanced cases: thenar wasting/weakness due to involvement of the motor branch of the median nerve
- ± Tinel's sign (paresthesia on percussion of nerve)
- ± Durkan's sign (paresthesia after pressure over carpal tunnel <30 s)
- ± Phalen's sign (wrist flexion induces symptoms)

Investigations
- generally a clinical diagnosis
- NCS and EMG studies may be used to objectively confirm the diagnosis if clinical history is atypical

Treatment
- avoid repetitive wrist and hand motion, wrist splints at night and when repetitive wrist motion required
- conservative: night-time splinting to keep wrist in neutral position
- medical: NSAIDs, local corticosteroids injection (relief from local corticosteroid injections is also diagnostic)
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: persistent signs and symptoms of median nerve compression not relieved by conservative management, or if motor function is compromised

Brachial Plexus

Etiology
- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumours, supernumerary ribs

Common Palsies

Table 23. Named Neonatal Palsies of the Brachial Plexus

Palsey	Location of Injury	Mechanism of Injury	Features
Duchenne-Erb Palsy	Upper brachial plexus (C5-C6)	Head/shoulder distraction (e.g. motorcycle)	"Waiter's tip deformity" (shoulder internal rotation, elbow extension and pronation, wrist flexion)
Klumpke's Palsy	Lower brachial plexus (C8-T1)	Traction on abducted arm	"Claw hand" May include Horner's syndrome

Differential Diagnosis of Adult-Acquired Brachial Plexus Palsies
- trauma (blunt, penetrating)
- thoracic outlet syndrome
  - associated with large cervical rib, anomalous first rib, strenuous arm work, and neck muscle hypertrophy
  - neurogenic: compression of brachial plexus, resulting in upper limb paresthesia, pain, and weakness
  - vascular: compression/thrombosis of subclavian artery/vein, resulting in pain; pallor and Raynaud's if arterial; swelling and cyanosis if venous
- tumour
  - schwannoma: well-defined margins enable total resection
  - neurofibromas: associated with neurofibromatosis type I
  - other: e.g. Pancoast syndrome (apical lung tumour)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

Investigations
- EMG
- MRI: gold standard for identifying soft tissue masses and nerve roots
- CT myelogram
- closed injuries: if avulsion suspected, then CT myelogram or MRI initially; otherwise, EMG/NCS 12 wk post-injury to assess healing progress
- open injuries: OR for exploration within a few days post-injury (once patient stable)

Management

Table 24. Management of Brachial Plexus Injuries*

Closed Injuries	Concussive/compressive	Often self-resolving (unless expanding mass, e.g. hematoma)
	Traction/stretch	If no continued insult, follow for 3-4 mo for improvement
	Obstetric palsy	Surgery if no significant improvement and/or residual paresis at age 6 mo
Open Injuries	Sharp or vascular injury	Explore immediately in OR

*All injuries listed require splinting as well as OT and PT consults to maintain ROM and function in the joint

Nerve Transfers
- indicated when nerve injury is close to the effector muscle or when other reconstructive options are not possible (e.g. preganglionic root avulsion, complete loss of motor, and/or sensory function); can also serve as adjunct to nerve grafting
- involves the use of an expendable nerve as a donor, such as one that supplies redundant innervation or one with less importance to daily functioning
- donor nerve serves to:
  - reconstruct the injured nerve closer to its effector muscle to better facilitate reinnervation, or
  - directly innervate effector muscle (neurotization)
- cortical plasticity involved in re-programming new nerve function
- can also serve as adjunct to nerve grafting
- both motor and sensory nerve transfers are possible, allowing motor and/or sensory restoration by neurotization
- three types of donors:
  - intraplexal (e.g. ulnar or median nerve fascicles)
  - extraplexal (e.g. contralateral C7 nerve root, intercostal nerve)
  - distal (e.g. radial nerve branches)

Craniofacial Injuries

Table 25. General Approach to Craniofacial Injuries

HISTORY		
Key Questions	Timing	Loss of consciousness
	Breathing difficulties	Confusion
	Neck pain	Headache
	Mechanism: high or low velocity (determines degree of damage)	
	Hearing changes	
	Vision changes: immediate or gradual loss in acuity, diplopia, ocular pain, pain with EOM, visual disturbances	
	Midface: breaking through the nose, depression of cheek bones, pain at the temporomandibular junction, deviation of nose, hearing loss	
	Mandible: malocclusion (loose or missing teeth)	
PHYSICAL EXAM		
	Structure	**Examination**
Observation	Facial structures	Look for facial asymmetry. If open lacerations, need to explore the wound under sterile conditions.
	Bruising or swelling	May indicate underlying skeletal injury (which can result in loss of function)
Palpation	Facial structures	Look at supraorbital bar, lateral orbital wall, infraorbital wall, malar prominence and mandible to reveal signs of crepitus, contour deformity, tenderness, step gap deformities, or midface instability.
Focused Exams	Eye exam	Changes to EOM, pain with EOM, signs of entrapment, diplopia, PERL, RAPD, proptosis, enophthalmos, racoon eyes
	Nasal exam	Tenderness, septal hematoma, rhinorrhea, septal deviation, difficulty breathing through nose
	Ear exam	Discharge, pain, tympanic membrane intact, hemotympanum, posterior auricular ecchymosis, hearing changes
	Oral exam	Malocclusion, open bite, intra-oral lacerations, hematoma, good oral hygiene, loose or damaged teeth, temporomandibular junction tenderness, uvula and tongue in midline
	Cranial exam	Bilateral sensation in CN V1, V2, V3, and CN VII distribution

Approach to Facial Injuries

- ATLS protocol
- inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve, bony injuries, septal hematoma, ocular involvement, etc.)
- tetanus prophylaxis
- radiological evaluation: CT scan with fine cuts of 1.5 mm through the orbit
- wound irrigation with NS/RL and removal of foreign materials
- conservative debridement of detached or nonviable tissue
- repair laceration(s) at the time of presentation with 4-0 nylon sutures when the patient's general condition allows
- consider intracranial trauma; rule out skull fracture
- management: most can wait ~5 d for swelling to decrease before ORIF required

Signs of Basal Skull Fracture
- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF otorrhea/rhinorrhea

Investigations
- CT (gold standard)
  - axial and coronal (specifically request 1.5 mm cuts): for fractures of upper, middle, and lower face
  - indicated for significant head trauma, suspected facial fractures, and preoperative assessment
- panorex radiograph: shows entire upper and lower jaw; best for isolated mandible fracture, but patient must be able to sit; however, if high clinical suspicion and negative panorex, CT should be done

Treatment Goals
- re-establish normal occlusion if occlusion is an issue
- normal eye function (extraocular eye movements and visual acuity)
- re-establish facial height and width to re-establish appearance
- consultation when indicated (dentistry, ophthalmology, neurosurgery)

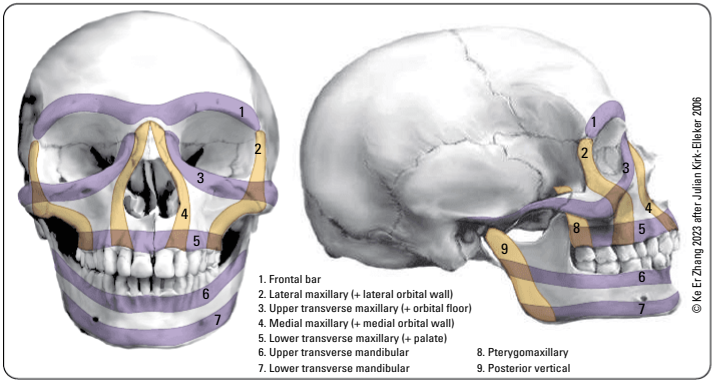
1. Frontal bar
2. Lateral maxillary (+ lateral orbital wall)
3. Upper transverse maxillary (+ orbital floor)
4. Medial maxillary (+ medial orbital wall)
5. Lower transverse maxillary (+ palate)
6. Upper transverse mandibular
7. Lower transverse mandibular
8. Pterygomaxillary
9. Posterior vertical
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Figure 32. Craniofacial horizontal and vertical buttresses

Mandibular Fractures

- two points of injury since it is a ring structure (includes fractures and dislocations)
- commonly at sites of weakness (condylar neck, angle of mandible)

Etiology
- anterior force: bilateral fractures
- lateral force: ipsilateral subcondylar and contralateral angle or body fracture
- note: classified as open if fracture into tooth bearing area (alveolus)

Clinical Features
- pain, swelling, difficulty opening mouth ("trismus")
- malocclusion, asymmetry of dental arch
- damaged, loose, or lost teeth
- palpable "step" along mandible
- numbness in CN V3 distribution
- intra-oral lacerations or hematoma (sublingual)
- chin deviating toward side of a fractured condyle

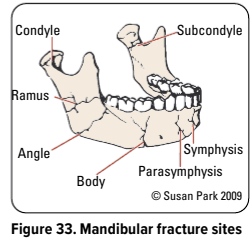

Figure 33. Mandibular fracture sites

Classification

Table 26. Mandibular Fracture Classifications by Anatomic Region

	Areas/Boundaries
Symphysis	Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible
Body	From the symphysis to the distal alveolar border of the third molar
Angle	Triangular region between the anterior border of the masseter and the posterosuperior insertion of the masseter distal to the third molar
Ramus	Part of the mandible that extends posterosuperiorly into the condylar and coronoid processes
Condylar*	Area of condylar process of mandible
Subcondylar	Area below the condylar neck (i.e. sigmoid notch) of the mandible
Coronoid Process	Area of the coronoid process of mandible

*Most common mandibular fracture type

Treatment
- maxillary and mandibular arch bars wired together (intermaxillary fixation) or ORIF (indications depend on whether fracture is unilateral/bilateral, etc.); ideally managed within 48 h
- antibiotics from initial presentation until at least 3 doses postoperatively; if late presentation, may consider treatment with antibiotics for an extended course

Maxillary Fractures

Table 27. Le Fort Classification

	Le Fort I	Le Fort II	Le Fort III
Alternative Name	Guérin fracture	Pyramidal fracture	Craniofacial disjunction
Type of Fracture	Horizontal	Pyramidal	Transverse
Structures Involved	Piriform aperture	Nasal bones	Nasofrontal suture
	Maxillary sinus	Medial orbital wall	Zygomaticofrontal suture
	Pterygoid plates	Pterygoid plates	Pterygoid plates
		Maxilla	Zygomatic arch
Anatomical Result	Maxilla divided into 2 segments	Maxillary teeth and midsection of the maxilla separated from upper face	Entire midfacial skeleton detached from cranial base

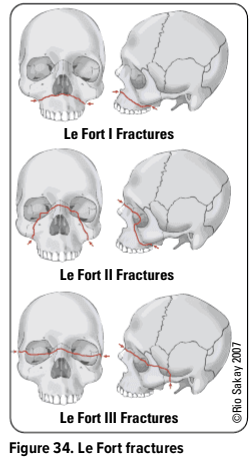

Figure 34. Le Fort fractures

Nasal Fractures

Etiology
- lateral force → more common
- anterior force → can produce more serious injuries
- most common facial fracture

Clinical Features
- epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum, crepitus, septal hematoma, respiratory obstruction, subconjunctival hemorrhage

Treatment
- treated for airway or cosmetic issues
- always inspect for, and drain, septal hematoma as this is a potential cause of septal necrosis and perforation – completed with small incision in the septal mucosa followed by packing
- closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with petroleum or non-adhesive gauze packing, nasal splint for 7 d
- best reduction immediately (<6 h) or when swelling subsides (5-7 d)
- rhinoplasty may be necessary later for residual deformity (30%)

Zygomatic Fractures

Classification
1. fracture restricted to zygomatic arch
2. depressed fracture of zygomatic complex (zygoma)
3. unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone, and orbital rim

Clinical Features
- 3 most common features (pathognomonic):
  - subconjunctival hemorrhage
  - periorbital ecchymosis (often associated with fractures of the orbital floor)
  - CN V2 numbness (infraorbital and superior dental nerves)

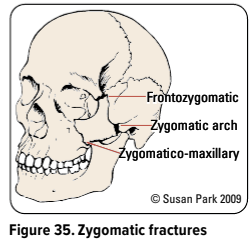

Figure 35. Zygomatic fractures

- flattening of malar prominence (view from above)
- pain over fractures on palpation
- palpable step deformity in bony orbital rim (especially inferiorly)
- ipsilateral epistaxis; trismus
- ophthalmologic evaluation if suspected globe injury

Treatment
- if non-displaced, stable, and no symptoms, then soft diet; no treatment necessary
- non-displaced zygomatic arch fractures can be elevated using Gillies approach (leverage on the anterior part of the zygomatic arch via a temporal incision) or Keen approach (elevation through upper buccal sulcus incision) only if arch is not comminuted
- if arch is comminuted, coronal incision and ORIF is required
- ORIF for displaced or unstable fractures of zygomatic complex (route is dependent on location of fracture)

Orbital Floor Fractures

- see Ophthalmology, OP42

Definition
- fracture of floor of orbit: may be a "pure blow-out fracture," which has an intact orbital rim, or can be associated with other fractures (orbital rim fracture and/or zygoma)

Etiology
- blunt force to eyeball (e.g. baseball or fist) → sudden increase in intraorbital pressure

Clinical Features
- restricted EOM (if muscle trapped)
- periorbital edema and bruising, subconjunctival hemorrhage
- ptosis, exophthalmos, exorbitism, enophthalmos, and hypoglobus may be present
- diplopia may be present
- orbital rim step-offs with possible infraorbital nerve anesthesia
- orbital entrapment
  - clinical diagnosis that is a surgical emergency
  - diplopia with straight gaze: unable to look up past neutral (entrapment of inferior rectus), limited EOM
  - severe pain or N/V with upward globe movement

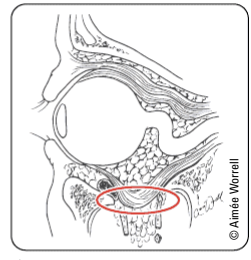

Figure 36. Blow-out fracture

Investigations
- CT (diagnostic): axial, coronal, and sagittal views – with fine cuts through orbit; rounding of inferior rectus can be a sign of orbital entrapment
- diagnostic maneuver for entrapment is forced duction test (pulling on inferior rectus muscle with forceps to ensure full ROM) under general anesthesia in the OR

Treatment
- surgical repair indicated if: entrapment, any size defect with enophthalmos (if patient is bothered by it), or persistent diplopia (>10 d)
- reconstruction of orbital floor with bone graft or alloplastic material (e.g. titanium meshes, MEDPOR®, MEDPOR TITAN®)
- after repair, many patients can have diplopia for several weeks

Complications
- persistent diplopia
- enophthalmos

Superior Orbital Fissure Syndrome
- fracture of SOF causing ptosis, proptosis, anesthesia in CN V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, VI)
- uncommon complication seen in Le Fort II and III fractures (1/130)
- recovery time reported as 4.8-23 wk following operative reduction of fractures

Orbital Apex Syndrome
- fracture through optic canal with involvement of CN II at apex of orbit
- symptoms are the same as SOF syndrome plus vision loss
- treatment is steroids or urgent decompression of fracture in optic canal (posterior craniotomy for decompression)

Traumatic Auricular Hematoma (Cauliflower Ear)

Definition
- trauma to the auricle that creates a subperichondrial hematoma that, if not corrected quickly, will form a permanent disfiguring nodularity known as "cauliflower ear"

Epidemiology
- higher prevalence in athletes who participate in contact risk sports (e.g. mixed martial arts, boxing); however, it is not exclusive to athletes

Clinical Features
- painless or slightly tender swelling of the upper aspect of the pinna
- becomes firmer and harder with time if left untreated
- colour is skin-coloured or slightly bluish

Differential Diagnosis
- relapsing polychondritis, auricular pseudocyst, epidermoid cyst

Treatment
- aspiration, I&D, and splinting of the auricular hematoma within 7 d (preferably first 72 h)

Breast

Anatomy

Vascular Supply

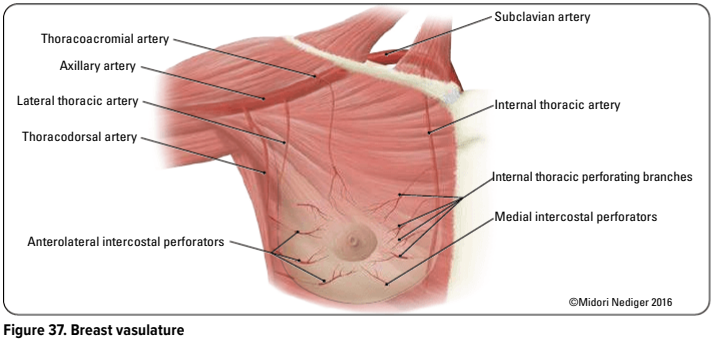

Figure 37. Breast vasulature

Innervation
- innervated in a dermatomal pattern from branches of the thoracic intercostal nerves (T3-6)
  - medially innervated from anterior cutaneous branches of I-VI intercostal nerves
  - laterally innervated from lateral cutaneous nerve branches of II-VII intercostal nerves
- lateral and upper portions of the breast innervated by lower fibres of the cervical plexus (C3, C4)
- NAC
  - supplied by anterior and lateral cutaneous branches of intercostal nerve IV
  - additional innervation by cutaneous branches of intercostal nerves III and VI

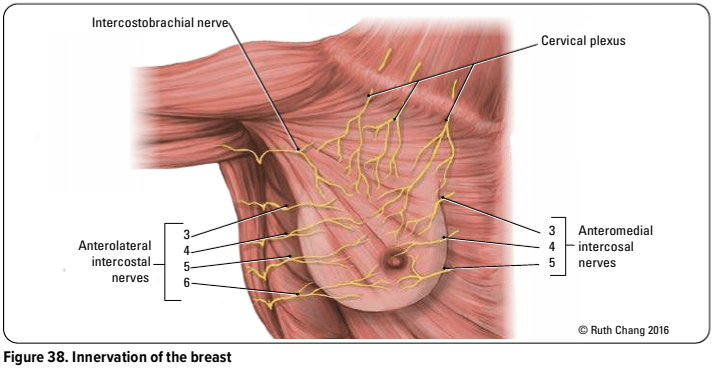

Figure 38. Innervation of the breast

Breast Reduction

Indications

- symptomatic (general symptoms)
  - musculoskeletal pain (back, bra strap location, neck), chronic headache, paresthesia in upper limb, rashes/irritation under the breast, breast discomfort, and physical impairment
- breast reduction methods can be classified based on pedicle (i.e. blood supply to the NAC) and skin resection pattern (i.e. the resultant scar)

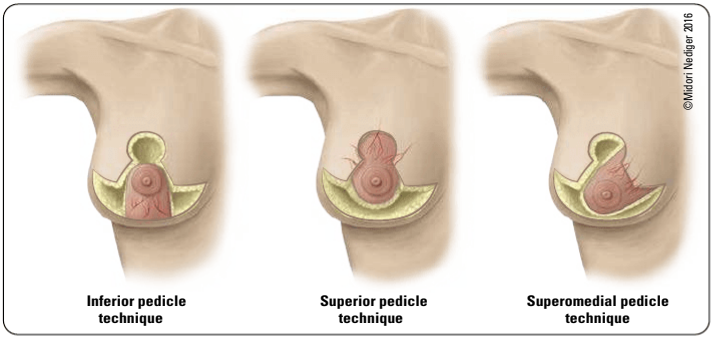

Figure 39. Inverted T ("Wise") pattern reduction

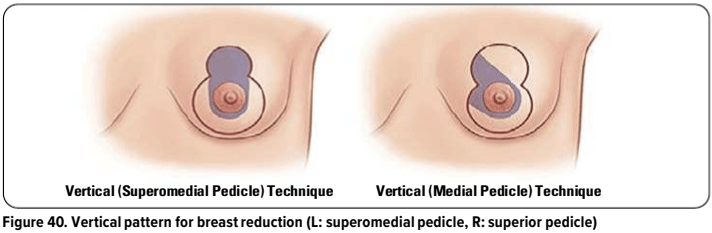

Figure 40. Vertical pattern for breast reduction (L: superomedial pedicle, R: superior pedicle)

Common Types of Pedicles

- inferior pedicle: derived from the fourth, fifth, and sixth intercostal perforators; most commonly used with the inverted T ("Wise") pattern reduction; versatile in small-large breast reduction
  - recommended pedicle width 6-8 cm, 8-10 cm in large breasts
- superior pedicle: derived from the internal mammary perforator of the second intercostal space
- medial pedicle: blood supplied by internal mammary perforators from third intercostal space and may have contribution from fourth intercostal space
- superomedial pedicle: incorporates the descending artery from the second intercostal space as the medial pedicle base extends superolaterally to the breast meridian
- bipedicle: used in McKissock's technique (well-vascularized dermal-parenchymal vertical bipedicle)

Table 28. Type of Skin Resections/Scar Options

	Indications	Description
Inverted T Pattern	Large breasts	Commonly used in association with inferior pedicle
	Breasts with poor quality skin that are challenging to remodel	Large portion of skin removed in horizontal and vertical direction
		Skin integrity important to shape and hold breast parenchyma
Vertical Pattern	Surgeon preference	Used in association with superior or medial pedicle
		Parenchyma needed to shape skin
		No horizontal scar

Complications

- NAC necrosis
- sensory alteration of nipple (may vary with type of pedicle) (may increase or decrease)
- unsatisfactory scarring, including hypertrophic or keloid scar
- wound healing complications (1-5% in healthy patients, higher in patients with elevated BMI)
- hematoma
- wound infection
- fat necrosis
- asymmetry of breasts and NAC
- potential inability to breastfeed

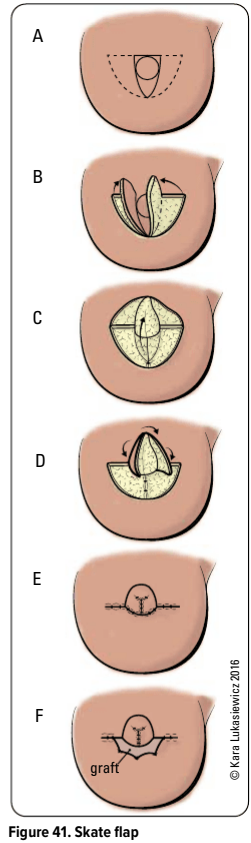

Figure 41. Skate flap
A) incision outline
B) elevation of wings
C) elevation of entire flap
D) caudal folding of flap
E) skate flap with primary closure of donor site
F) with skin graft

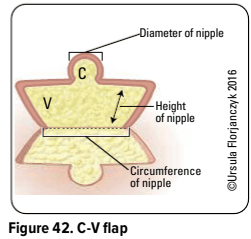

Figure 42. C-V flap

Mastopexy (Breast Lift)

Definition
- aesthetic procedure of the breast used to correct breast ptosis by modifying the contour and size of the breast along with elevating the position of the nipple

Clinical Grading of Ptosis (Regnault Ptosis Grade Scale)
1. minor ptosis (Grade 1)
   - nipple at inframammary fold
2. moderate ptosis (Grade 2)
   - nipple below inframammary fold, but above lower breast contour
3. severe ptosis (Grade 3)
   - nipple below inframammary fold and at lower breast contour
4. glandular ptosis/pseudoptosis
   - ptosis of the lower pole of the breast where the NAC is at or above the inframammary fold

Choice of Incision
- mastopexy can be performed through the same incisions as breast reductions

Breast Augmentation

Definition
- procedure designed to increase the size of the breast

Choice of Incision
- position of incision individualized since no single incision is best for all patients
- 3 commonly used types of incision: periareolar, inframammary crease, transaxillary

Type of Implant
- silicone or saline-filled
- subclassified into various styles of surface and shape

Location of Implant
- implants are commonly placed in the following positions:

1. submuscular
   - implant placed deep to the pectoralis major muscle
   - most commonly in patients that do not have enough tissue to cover the implant
2. subglandular
   - implant placed deep to glandular breast tissue but superficial to muscle
3. subfascial
   - implant placed below the pectoralis fascia

Complications
- hematoma, infection, capsular contracture, leakage rupture, aesthetic deformity
- breast implant illness
- BIA-ALCL
  - increased risk of BIA-ALCL with textured implants
  - presents as sudden onset of pain without injury or as sudden onset of seroma on average 7-8 yr after use of a textured implant for reconstruction or augmentation purposes
  - etiology: several theories, including implant-induced chronic inflammation, chronic biofilm, reaction to silicone shards, and causes not yet determined
  - risk estimated by Health Canada to be 1/3565 for Allergan Biocell® macro-textured implants and 1/16703 for Mentor® Siltex® micro-textured implants (Health Canada safety alert RA-70045)
  - management: en bloc resection of the implant and capsule; standard secondary therapy includes brentuximab
- favourable clinical outcome if detected and treated early

Gynecomastia

Definition
- benign enlargement of the male breast due to proliferation of the glandular tissue

Clinical Classification
- gynecomastia can be further classified into:

1. idiopathic
2. physiologic
   - neonatal: circulating maternal estrogens via placenta
   - pubertal: relative excess of plasma estradiol vs. testosterone
   - elderly: decreased circulating testosterone, peripheral aromatization of testosterone to estrogen
3. pathologic
   - endocrinopathies: excess estrogen, androgen deficiency, deficient testosterone production or action
   - tumours
   - chronic disease: liver cirrhosis, renal

- congenital/genetic: Klinefelter's syndrome, androgen resistance

4. pharmacologic
   - drugs that may interfere with estrogen-testosterone balance including:
     - hormones (estrogens, gonadotropins, exogenous steroids)
     - antiandrogens
     - androgen receptor antagonists (steroidal and non-steroidal)
     - androgen synthesis inhibitors (5α-reductase inhibitors)
     - antigonadotropins (GnRH analogs, estrogens)
     - recreational drugs (cannabis, heroin, amphetamines)
     - antihypertensives (spironolactone)
5. massive weight gain
   - for physical exam, investigations, and medical management, see Endocrinology, E54

Surgical Options

- surgery is the accepted method of management for gynecomastia
- surgery addresses the three components: breast tissue, fat, skin
- often involves a combination of liposuction (to remove the fatty portion) and surgical excision through a small periareolar incision (to remove the glandular component)
- patients with significant skin excess may require skin excision as well

Breast Reconstruction

- use of alloplastic devices or autogenous tissue to reconstruct breast after cancer or trauma
- reconstruction can be performed immediately (at the same time as mastectomy) or delayed (as a separate surgery months or years after initial surgery)
  - lymphedema may result after breast cancer treatment (e.g. axillary lymph node dissection, radiation) see Vascular Surgery, VS11
- there are alloplastic and autogenous methods of reconstruction, each with its advantages and disadvantages

Table 29. Immediate Reconstruction vs. Delayed Reconstruction

	Advantages	Disadvantages
Immediate Reconstruction	Generally best aesthetic outcome; may preserve nipple if oncologically safe Does not require creation of additional skin Tissues are not damaged from scarring	Mastectomy flap viability can compromise outcome Longer surgical time
Delayed Reconstruction	Good option for patients unable to have immediate reconstruction For patients who may be getting radiotherapy and undetermined post-surgery oncologic treatment Provides option of contralateral surgery with reconstruction, if required (i.e. contralateral cancer, genetic marker for disease)	Loss of skin, volume, lateral border of breast, and natural landmarks, including inframammary fold (makes surgery more challenging) Resection of irradiated/scarred skin and associated wound healing complications, including risk of reconstructive failure Likely requires more stages than immediate reconstruction for completion

Table 30. Alloplastic Reconstruction vs. Autogenous Reconstruction

		Advantages	Disadvantages
Alloplastic Reconstruction	**Single stage direct to implant (DTI)**	Shorter surgery May give a more complete or final result	Size restriction in reconstruction Very few patients meet criteria: Grade 1 ptosis, small breast, skin-sparing mastectomy
	Two stage reconstruction with expander and implant	Less tension on mastectomy flaps compared to single-stage reconstruction with implants Ability to increase amount of skin and avoid use of flap Some patient control over final outcome	Requires multiple OR procedures and clinic visits Waiting time between first and second stages Requires post-surgical procedures (patient to come to clinic for inflations) Size of reconstruction limited to mastectomy flap size and vascularity
	Acellular dermal matrix and implant	Can cover areas of implant or tissue expander and place it above muscle (no muscle dissection required) Can create larger submuscular pocket for bigger device	Animation if submuscular
Autogenous Reconstruction	**Transverse Rectus Abdominis Myocutaneous (TRAM) flap**	Can be done as a free tissue transfer or as a pedicled TRAM Provides a good amount of tissue for transfer in most patients Similar to well concealed "tummy tuck" scar	Abdominal scar Volume depends on patient's donor site Weakness in rectus abdominis Pedicled TRAM: Higher bulge rates Higher rate of flap necrosis Free TRAM: Requires preparation of recipient vessels and microsurgical anastomosis
	DIEP	Method spares rectus abdominis muscle and fascia and should theoretically preserve innervation and continuity of abdominal wall	Dependent on amount of abdominal tissue available Abdominal scar
	Latissimus dorsi flap	Reliable pedicle Provides skin and muscle Possible to do muscle sparing procedure without flap compromise Good option if abdominal tissue not sufficient	Hollowness at harvest site Shoulder weakness or impaired shoulder range of motion Dorsal hernia

Table 30. Alloplastic Reconstruction vs. Autogenous Reconstruction

	Advantages	Disadvantages
SGAP	Upper part of buttock Muscle-sparing Can remove extra tissue from flanks to reduce abdominal circumference	Short pedicle length More technically challenging than TRAM and DIEP
IGAP	Lower part of buttock Muscle-sparing	Contour of buttock is affected Short pedicle length More technically challenging than TRAM and DIEP
TUG	Good option if abdominal and buttock tissue not sufficient Scar is well hidden within groin crease Gracilis muscle not critical for strength	Not amenable to large breast reconstruction Short pedicle length Potential damage to lymphatic drainage of leg
PAP	Good option if abdominal and buttock tissue not sufficient Muscle-sparing Scar is hidden within/beneath gluteal sulcus	Not amenable to large breast reconstruction May have altered sensation in posterior thigh

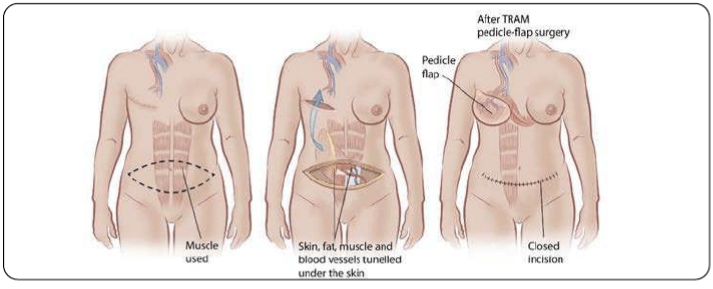

Figure 43. TRAM pedicle-flap
Image reprinted with permission from the Canadian Breast Cancer Network: https://cbcn.ca/en/autologous-reconstruction

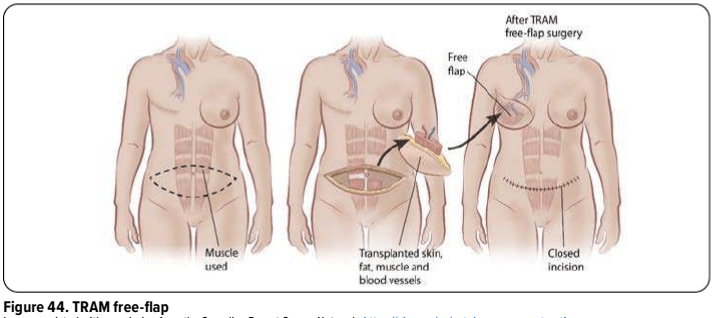

Figure 44. TRAM free-flap
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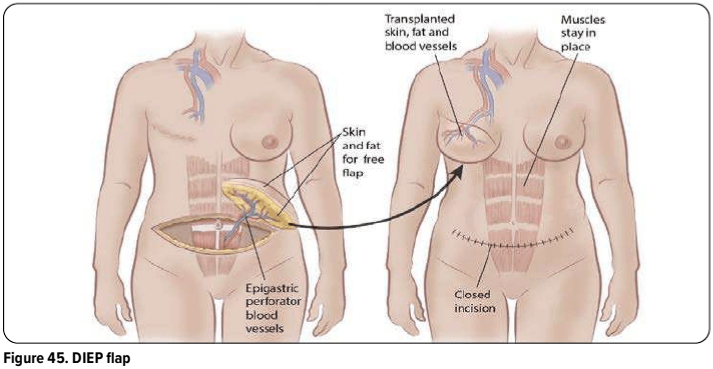

Figure 45. DIEP flap
Image reprinted with permission from the Canadian Breast Cancer Network: https://cbcn.ca/en/autologous-reconstruction

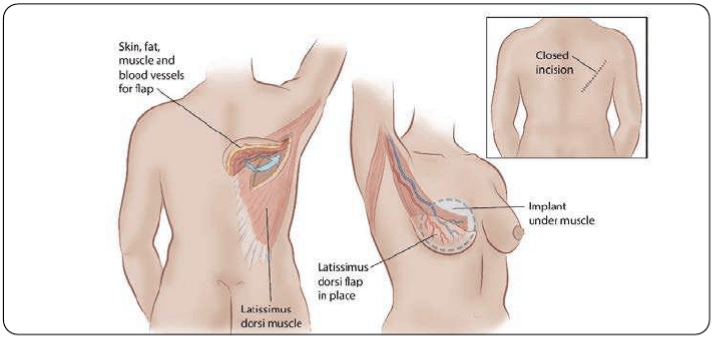
Skin, fat, muscle and blood vessels for flap
Closed incision
Implant under muscle
Latissimus dorsi flap in place
Latissimus dorsi muscle

Figure 46. Latissimus dorsi flap
Image reprinted with permission from the Canadian Breast Cancer Network: https://cbcn.ca/en/autologous-reconstruction

Nipple Areolar Complex Reconstruction

- nipple reconstruction is usually done as the final step when the patient is satisfied with breast mound creation
- reconstruction can be performed with local anesthetic since many patients have decreased sensation in the mastectomy or breast flaps
- it can be done by either a flap, graft, or 3D tattoo

Table 31. Types of Nipple Reconstruction

	Description	Advantages	Disadvantages
Skate Flap	Pedicle elevated above breast mound Lateral aspects of flap are wrapped around central aspect of flap Defect mainly closed by skin graft	Low complication rates	Loss of projection Donor site morbidity May have loss of projection over time Skin graft required
C-V Flap	Utilizes C flap and two V flaps for nipple reconstruction Diameter of C flap becomes diameter of reconstructed nipple Width of V flaps dictate projection of reconstructed nipple C-V flap closed with primary closure	No grafts required	Loss of projection Nipple size limited by flap dimensions May have loss of projection over time Tattooing required to match natural areola
Nipple Graft	Tissue commonly from contralateral nipple (nipple share) or labia Two methods for nipple graft: • Distal aspect of nipple removed transversely and defect closed with purse string suture • Nipple divided in half longitudinally, folded over, and closed with primary closure	Nipple share is an excellent option in patients with contralateral nipple projection >1 cm	Loss of projection Donor site morbidity Decreased contralateral nipple sensation Necrosis of graft or donor nipple

Table 32. Types of Areolar Reconstruction

	Description	Advantages	Disadvantages
Tattoo*	Conducted 3-4 mo after nipple reconstruction when most of the projection has stabilized	Can provide more accurate colour matching with limited morbidity	May require touch-ups due to pigment fading over time with skin sloughing
Skin Graft*	Full thickness skin grafts, commonly from inner aspect of thigh or opposite areola	Provides texture and pigment resembling a natural areola	Donor site morbidity

* Tattoo and skin grafting can be used in conjunction

Aesthetic Surgery

Aesthetic Procedures

Table 33. Aesthetic Procedures

Location	Procedure	Description
Head/Neck	Hair transplants	Aesthetic improvement of hair growth patterns using hair follicle grafts or flaps
	Otoplasty	Surgical reconstruction of external ear
	Forehead/brow lift	Surgical procedure to lift the forehead and eyebrows
	Rhytidectomy	Surgical procedure to reduce wrinkling and sagging of the face and neck; "face lift"
	Blepharoplasty	Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin ± fat pads
	Rhinoplasty	Surgical reconstruction of the nose ± nasal airway
	Genioplasty	Chin augmentation via osteotomy or synthetic implant to improve contour
Skin	Chemical peel	Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration
	Dermabrasion	Skin resurfacing with a rapidly rotating abrasive tool; often used to reduce scars, irregular skin surfaces, and fine lines
	Laser resurfacing	Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening; often used to reduce scars and wrinkles
	Injectable fillers	An injectable substance is used to decrease facial rhytids; can augment lips to create fuller appearance; substances include: collagen, fat, hyaluronic acid, and calcium hydroxyapatite (most common substances include hyaluronic acid and fat)
Other	Abdominoplasty	Removal of excess skin and repair of rectus muscle laxity (rectus diastasis); "tummy tuck"
	Calf augmentation	Augmentation of calf muscle with implants
	Liposuction	Surgical removal of adipose tissue for body contouring (not a weight loss procedure)

Gender-Affirming Surgery (Transition-Related Surgery)

- ensure appropriate use of gender pronouns
- some procedures require 1 yr trial of hormone therapy, preoperative letters of evaluation, and documentation from mental health professionals as outlined by the World Professional Association for Transgender Health Standards of Care – Version 7 guidelines

Table 34. Surgical Options for Transgender Women

Procedure	Description	Follow-Up
Breast Augmentation	Implant-based, fat-grafting, or combined surgery to increase breast size	Surveillance for implant rupture Adhere to breast cancer screening guidelines in addition to gender-specific medical maintenance
Contouring Procedures	Altering fat distribution in distinguishing regions of the body (abdomen, flank, hip, and buttock) using liposuction or fat-grafting (limited by availability of autologous fat)	Short-term restrictions on placing body weight on fat-grafted areas (<2 wk) 100% of injected fat volume not maintained long-term
Facial Feminization	± Hairline surgery ± Forehead augmentation or osteotomy ± Rhinoplasty ± Genioplasty (implant alone is usually not sufficient)	Hair transplant may be needed in adjunct May have altered lip sensation and altered sensation of lower incisors with genioplasty
Chondrolaryngoplasty	Cartilage removal to reduce thyroid cartilage size	Risk of long-term hoarseness based on anatomical proximity of recurrent laryngeal nerve to site of surgery
Vocal Cord Surgery	Alteration of vocal cord length to increase vocal pitch	Not all procedures are permanent (i.e. cricothyroid approximation) Some procedures may narrow airway (i.e. anterior glottal web formation) Not guaranteed to achieve exact desired pitch change
Vaginoplasty	see Urology, *Transition-Related Surgeries*, U47	

Table 35. Surgical Options for Transgender Men

Procedure	Description	Follow-Up
Chest Masculinization	Most common technique is double incision free nipple graft technique	Loss of nipple sensation May need liposuction for patients with excess subcutaneous tissue
Contouring Procedures	see *Table 34*	

Table 35. Surgical Options for Transgender Men

Procedure	Description	Follow-Up
Facial Masculinization	± Forehead augmentation ± Maxillary augmentation ± Mandibular augmentation ± Rhinoplasty ± Genioplasty	May have altered lip sensation and altered sensation of lower incisors with genioplasty
Thyroid Cartilage Enhancement	Cartilage added to increase thyroid cartilage prominence	Risk of vocal cord paralysis due to surgery
Vocal Cord Surgery	Alteration of vocal cord length to decrease vocal pitch	Not guaranteed to achieve exact desired pitch change
Phalloplasty, Metoidioplasty	see Urology, *Transition-Related Surgeries*, U47	

- for further information on gender-affirming surgical techniques, see Urology, *Transition-Related Surgeries*, U47

Pediatric Plastic Surgery

Craniofacial Anomalies

Table 36. Pediatric Craniofacial Anomalies

	Definition	Epidemiology	Clinical Features	Treatment
Cleft Lip	Failure of fusion of maxillary and medial nasal processes	1 in 1000 live births (increased incidence in Asian individuals, decreased incidence in individuals of African descent) M:F=2:1	Classified as incomplete/complete and unilateral/bilateral; 2/3 cases: unilateral, left-sided, male	Surgery (3 mo): Millard, or Fisher (additional corrective surgeries usually required later on - especially for nasal deformity
Cleft Palate	Failure of fusion of lateral palatine/median palatine processes and nasal septum	Isolated cleft palate: 0.5 in 1000 (no racial variation) F>M 4% chance of cleft if one parent or sibling have cleft 17% chance of cleft if both sibling and parent have cleft	Classified as incomplete/complete and unilateral/bilateral Isolated (common in females) or in conjunction with cleft lip (common in males)	Special bottles for feeding SLP Surgery (6-9 mo): Von Langenbeck or Furlow Z-Plasty ENT consult – often recurrent otitis media, requiring myringotomy tubes
Craniosynostosis		1 in 2000 live newborns; M:F=52:48 Syndromes include: Crouzon's, Apert's, Saethre-Chotzen, Carpenter's, Pfeiffer's, Jackson-Weiss, and Boston-type syndromes	Primary (no known cause), or secondary (associated with a known cause or syndrome)	Multidisciplinary team (including neurosurgery, ENT, genetics, dentistry, pediatrics, SLP) The type, timing, and procedure are dependent on which sutures (lambdoid, sagittal, etc.) are involved Early surgery prevents secondary deformities

Congenital Hand Anomalies

Table 37. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

Classification	Example	Features	Treatment
Failure of Formation	Transverse absence (congenital amputation)	At any level (often below elbow/wrist)	Early prosthesis
	Longitudinal absence (phocomelia)	Absent humerus Thalidomide association	
	Radial deficiency (radial club hand)	Radial deviation Thumb hypoplasia M>F	Physiotherapy + splinting Soft tissue release if splinting fails Distraction osteogenesis (Ilizarov distraction) ± wedge osteotomy Tendon transfer Pollicization
	Thumb hypoplasia	Syndromes include: Fanconi anemia, Holt-Ogram, and CHARGE syndromes. Degree ranges from small thumb with all components to complete absence	Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger
	Ulnar club hand	Rare, compared to radial club hand Stable wrist	Splinting and soft tissue stretching therapies Soft tissue release (if above fails) Correction of angulation (Ilizarov distraction)

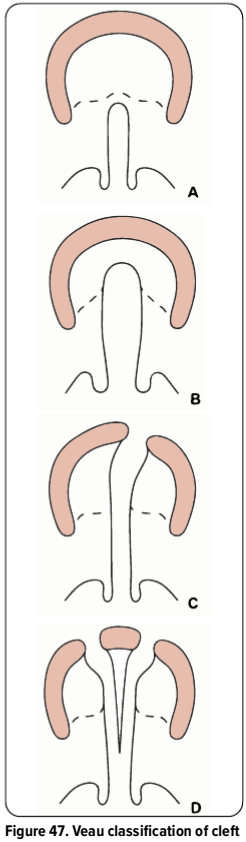

Figure 47. Veau classification of cleft lip and palate

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Table 37. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

Classification	Example	Features	Treatment
	Cleft hand	Autosomal dominant Often functionally normal (depending on degree)	First web space syndactyly release Osteotomy/tendon transfer of thumb (if hypoplastic)
Failure of Differentiation/ Separation	Syndactyly	Syndromes include: Apert, Poland, and Holt-Oram syndromes 1 in 3000 live births M:F=2:1	Surgical separation before 6-12 mo of age May require a skin graft to cover the fingers Usually good result
	Symbrachydactyly	Short fingers with short nails at fingertips	Digital separation Webspace deepening
	Camptodactyly	Congenital flexion contracture (usually at PIP, especially 5th digit)	Early splinting Volar release Arthroplasty (rarely)
	Clinodactyly	Radial or ulnar deviation Often middle phalanx	None (usually); if severe, osteotomy with grafting
Duplication	Polydactyly	Congenital duplication of digits May be radial (increased in Asian individuals and Indigenous peoples) or central or ulnar (increased in individuals of African descent)	Amputation of least functional digit Usually >1 yr of age (when functional status can be assessed)
Overgrowth	Macrodactyly	Rare	None (if mild) Soft tissue/bony reduction
Undergrowth	Brachydactyly	Short phalanges	Removal of nonfunctional stumps Osteotomies/tendon transfers Distraction osteogenesis Phalangeal/free toe transfer
	Symbrachydactyly Brachysyndactyly	Short webbed fingers	As above + syndactyly release
Constriction Band Syndrome	Amniotic (annular) band syndrome	Variety of presentations	Urgent release for acute, progressive edema distal to band in newborn Other reconstruction is case specific
Generalized Skeletal Abnormality	Achondroplasia, Marfan syndrome, Madelung's deformity	Variety of presentations	Treatment depends on etiology

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PS Psychiatry

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Acronyms

5-HT	serotonin	DZ	dizygotic	MET	motivational enhancement therapy	PDD	pervasive developmental disorder
ACh	acetylcholine	ECT	electroconvulsive therapy	MI	motivational interviewing	PTSD	post-traumatic stress disorder
ACT	assertive community treatment	EPS	extrapyramidal symptoms	MSE	mental status examination	rTMS	repetitive transcranial magnetic stimulation
ADHD	attention deficit hyperactivity disorder	ERP	exposure with response prevention	MST	magnetic stimulation therapy	SGA	second generation antipsychotics
ADL	activities of daily living	GAD	generalized anxiety disorder	MZ	monozygotic	SIADH	syndrome of inappropriate antidiuretic hormone secretion
AN	anorexia nervosa	GMC	general medical condition	NA	Narcotics Anonymous	SNRI	serotonin and norepinephrine reuptake inhibitors
ASD	autism spectrum disorder	IPT	interpersonal therapy	NMS	neuroleptic malignant syndrome	SS	serotonin syndrome
ASPD	antisocial personality disorder	IADL	instrumental activities of daily living	NOS	not otherwise specified	SSRI	selective serotonin reuptake inhibitor
BN	bulimia nervosa	MBCT	mindfulness-based cognitive therapy	OCD	obsessive-compulsive disorder	TCA	tricyclic antidepressant
CBT	cognitive behavioural therapy	MBSR	mindfulness-based stress reduction	OCP	oral contraceptive pill	TD	tardive dyskinesia
CD	conduct disorder	MDD	major depressive disorder	OCPD	obsessive-compulsive personality disorder	XR	extended-release
CRA	community reinforcement approach	MDE	major depressive episode	ODD	oppositional defiant disorder		
CT	community treatment order			PCP	phencyclidine		
DA	dopamine			PD	personality disorder		
DBT	dialectical behavioural therapy						

Psychiatric Assessment

History

Introduction
- name, role, purpose, circumstances (i.e. approximate time)
- limits of confidentiality (i.e. safety of dependents, harm to self or others)

Identifying Data
- necessary: name, age, gender (preferred pronouns), living situation (accommodation, independently, or with others), marital/relationship status, children, source of income/support, occupation, drug/therapy coverage, current mental health supports (i.e., therapist, case worker, etc)
- adjunct: outpatient/inpatient, referral source, known/unknown to provider

Chief Complaint
- in patient's own words, with duration of symptoms

History of Present Illness
- context: events, problems, stressors, losses, changes
- symptoms: onset, duration, intensity, progression, fluctuation with day/season
- impact on functioning: social, occupational, ADL/IADLs, personal care/survival
- coping strategies, treatments, personal/professional supports
- reason for seeking help that specific day
- prior episodes/experiences, longitudinal course (duration/frequency)
- last period of wellness, changes to usual personality when unwell
- opinions about cause/nature of concerns, willingness to engage, hopes/expectations of treatment

Screening Questions for Major Psychiatric Disorders
- Have you been feeling down, depressed, or hopeless?
- Do you feel anxious or worry about things?
- Has there been a time in your life where you have felt euphoric, extremely talkative, had a lot of energy, and a decreased need for sleep?
- Do you see or hear things that you think other people cannot?
- Have you ever thought of harming yourself or killing yourself?

Psychiatric Functional Inquiry
- mood: depression, mania
- other: trauma, obsessions/compulsions, disordered eating
- anxiety: worries, panic attacks, phobias, or social anxiety
- psychosis: hallucinations, delusions
- safety/risk: self (suicidal ideation/intent/plan (see *Suicide, PS5*), self-harm, neglect), others (homicide, aggression, violence), dependents (children, elderly, disabled, pets), driving, cooking/fires

Psychiatric Functional Inquiry

MOAPS
Mood
Other (medical problems and substance use)
Anxiety
Psychosis
Safety

Past Psychiatric History
- previous psychiatric diagnoses, episodes (e.g., of depression, mania, etc.), and mental health contacts
  - if applicable, including details on triggers, duration, symptoms, and factors leading to resolution of prior episodes, focusing on most severe and most recent episodes
- hospitalizations: approximate total, date of last discharge
- emergency department visits (for mental health crisis)
- suicide attempts: number, severity, medical intervention, most recent
- self-harming behaviour (cutting)
- aggression/violence, legal (charges)
- treatments: pharmacological and non-pharmacological (effectiveness, side effects)

Substance Use History
- type: tobacco, cannabis, alcohol, caffeine, other (stimulants, hallucinogens, prescription drugs, gambling/online)
- use: first, typical, last, periods of abstinence
- withdrawal symptoms (i.e. seizures, delirium tremens)
- previous treatments: counselling, detox, groups
- impact on symptoms, motivation to change

Past Medical/Surgical History
- all medical, surgical, neurological (i.e. head trauma, seizures) conditions/illnesses
- allergies

Medications
- names, doses, frequency
- adherence, effectiveness, side effects
- over the counter, supplements

Family Psychiatric/Medical History
- diagnoses, treatments, hospitalizations, suicide attempts, substance use, legal
- perceptions regarding mental illness, engagement with treatments
- if relevant: any past medical or genetic illness

Always Remember to Ask About Abuse
See Family Medicine, FM29

Past Personal/Developmental History (as relevant)
- birthplace, immigration history (if applicable), ethnicity/nationality, religion/spirituality
- family members: ages, occupations, personalities, quality of relationships
- history of verbal, physical, or sexual abuse
- prenatal and perinatal history: desired vs. unplanned pregnancy, maternal and fetal health, domestic violence, maternal substance use and exposures, complications of pregnancy/delivery
- early childhood to age 3: developmental milestones, temperament, family stability, primary caregivers/attachment figures
- middle childhood to age 11: school performance, peer relationships, bullying, activity/attention level, behavioural challenges
- late childhood to adolescence: school performance, drugs/alcohol, legal problems, peer and family relationships, extra-curriculars
- sexuality: puberty, gender identity, sexual orientation, sexual functioning/experiences, romantic relationships
- adulthood: education, employment, relationships
- hobbies, interests, sources of meaning, strengths, accomplishments, aspirations, hopes

Collateral History
- source, details provided (comment on any inconsistencies between collateral and patient report if applicable)

Mental Status Exam

Mental Status Exam

ASEPTIC
Appearance and behaviour
Speech
Emotion (mood and affect)
Perception
Thought content and process
Insight and judgment
Cognition

General Appearance
- age (chronological vs. apparent), gender, ethnicity
- posture, grooming, hygiene, manner of dress, body habitus, distinguishing features
- eye contact, facial expression, alertness
- attitude: polite, friendly, collaborative, uncooperative, guarded/suspicious, evasive, agitated, aggressive/hostile
- reliability (consistency, congruent with collateral), ease of building rapport
- gait, psychomotor changes (slowing/agitation), tics, tremors, tardive dyskinesia, dystonia, catatonia

Speech
- rate (i.e. pressured, slowed), rhythm, volume, tone, quantity, spontaneity, latency, language fluency, articulation

The MSE is analogous to the physical exam. It focuses on current signs, affect, behaviour, and cognition

Mood and Affect
- mood: subjective emotional state (in patient's own words)
- affect: objective emotional state inferred from emotional responses to stimuli; described in terms of
  - quality (euthymic, depressed, elevated, anxious, irritable)
  - range (full, restricted, flat, blunted)
  - stability (continuum from fixed to labile)
  - mood congruence (inferred by comparing the patient's subjective mood with their affect)
- many clinicians use a 0-10 scale (0: worst; 10: best) when rating mood to get a subjective norm for each patient that can help to monitor changes over time and with treatment

Spectrum of Affect
Full > Restricted > Blunted > Flat; quality (euthymic, depressed, anxious, elated)

Perception
- hallucination: sensory perception in the absence of appropriate stimuli that is similar in quality to a true perception
  - auditory (most common), visual, gustatory, olfactory, tactile
- illusion: misperception of a real external stimulus (i.e. mistaking a coat on a rack as a person late at night)
- depersonalization: change in self-awareness such that the person feels unreal, distant, or detached from their body, and/or unable to feel emotion
- derealization: feeling that the world/outer environment is unreal

There is poor correlation between clinical impression of suicide risk and frequency of attempts

Thought Process/Form
- coherence (coherent, incoherent)
- stream
  - goal-directed: clearly answers questions in a linear, organized, logical fashion
  - circumstantial: speech that is indirect and delayed in reaching its goal; eventually comes back to the point
  - tangential: speech is oblique or irrelevant; does not come back to the original point
  - loosening of associations/derailment: illogical shifting between topics
  - flight of ideas: quickly skipping from one idea to another where the ideas are marginally connected, usually associated with racing thoughts in mania
  - word salad: jumble of words lacking meaning or logical coherence
- perseveration: repetition of the same verbal or motor response to stimuli
- echolalia: repetition of phrases or words spoken by someone else
- thought blocking: sudden cessation of flow of thought and speech
- clang associations: speech based on sound such as rhyming or punning
- neologism: use of novel words or of existing words in a novel fashion

Thought Content
- major themes discussed by patient
- suicidal ideation/homicidal ideation: frequency and pervasiveness of thoughts, plan, intent, active vs. passive, protective factors
- preoccupations, ruminations: reflections/thoughts at length, not fixed or false
- obsession: recurrent and persistent thought, impulse, or image which is intrusive or inappropriate and unwanted
  - cannot be stopped by logic or reason
  - causes marked anxiety and distress
  - common themes: contamination, orderliness, sexual, pathological doubt/worry/guilt
- magical thinking (i.e. superstition, belief that thinking something will make it happen), normal in children and certain cultures
- ideas of reference: similar to delusion of reference, but less fixed (the reality of the belief is questioned)
- overvalued ideas: unusual/odd beliefs that are not of delusional proportions
- first rank symptoms of schizophrenia: thought insertion/withdrawal/broadcasting (all delusional ideas)
- delusion: a fixed false belief that is out of keeping with a person's cultural or religious background and is firmly held despite incontrovertible proof to the contrary

Insight
- ability to realize that they have a mental health concern and to appreciate its implications as it relates to functioning and benefits of treatment: none, limited, partial, or full

Judgment
- recent behaviours as they relate to safety, social functioning, treatment decisions

Cognition
- level of consciousness (alert, reduced, obtunded)
- orientation: time, place, person
- memory: immediate, recent, or remote
- global evaluation of intellect (below average, average, or above average, in keeping with person's education)
- intellectual functions: attention, concentration, calculation, abstraction (proverb interpretation, similarities test), language, communication
- Mini Mental Status Exam (MMSE)/Montreal Cognitive Assessment (MoCA) useful as standard screening assessments of cognition

Assessment and Plan

Historical Multiaxial Model
- since Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), this model is no longer used for psychiatric diagnosis. Instead, relevant psychiatric and medical diagnoses are simply listed. Nevertheless, we offer it here as a possible framework for psychiatric patient assessment, as many physicians still employ it

Multiaxial Assessment
- Axis I: DSM-5 diagnoses (preferred and differential)
- Axis II: personality disorders, intellectual disability
- Axis III: medical conditions potentially relevant to understanding/management of the mental disorder
- Axis IV: psychosocial and environmental issues
- Axis V: Global Assessment of Functioning (GAF, 0 to 100) incorporating effects of axes I to IV

Cognitive Assessment
Use MMSE to assess
- Orientation (time and place)
- Memory (immediate and delayed recall)
- Attention and concentration
- Language (comprehension, reading, writing, repetition, naming)
- Spatial ability (intersecting pentagons)

Gross screen for cognitive dysfunction: Total score is out of 30; <26 abnormal, 20-25 mild, 10-19 moderate, <10 severe

The key to differentiating between obsessions and delusions is that obsessions are usually ego dystonic, meaning unwanted and not fitting in with a person's goals and self-image, while delusions are ego syntonic

Delusions (Absolute Beliefs)
Persecutory: belief that others are trying to cause harm to you
Reference: interpreting ordinary, regular events/celebrities as having direct reference to you
Erotomania: belief that another is in love with you
Grandiose: belief that he or she has special powers, talents, or abilities
Religious: belief of receiving instructions/powers from a higher being; of being a higher being
Somatic: belief that you have a physical disorder/defect
Nihilistic: belief that things do not exist; a sense that everything is not real

Assessing Insight and Judgment
Insight
- Acknowledgment of symptoms as a departure from baseline or source of suffering
- Attribution of symptoms to illness or acceptance as such explanation as part of the process
- Acknowledgement of need for treatment (Why are you in the hospital? Why are you taking this medication? What would happen if you stopped taking it?)

Judgment
Can be observed from collected history and patient's appearance and actions. Are they:
- Dressed appropriately for the weather?
- Acting appropriately in the given situation?
- Taking care of self and/or dependents?

After History and MSE, the assessment and plan is recorded

Assessment/Problem Formulation

- identify predominant symptom cluster (mood, anxiety, psychosis) that causes the most distress/interference and persists when other symptom categories are not present (i.e. psychosis in the absence of mood symptoms)
- dominating symptoms will direct differential
- consider current issues as they relate to an individual across the three domains: biological, psychological, and social
- for each category: predisposing, precipitating, perpetuating, and protecting factors are considered

Always rule out substance use and other medical causes before considering psychiatric causes

Approach to Management

- consider short-term and long-term, and three types: biological (i.e. pharmacotherapy, ECT), psychological (i.e. CBT), and social (i.e. supports, finance/employment/return to work, housing, social activity, recreation, medication/psychotherapy coverage)

Suicide

Importance

- must be screened for in every encounter; part of risk assessment along with violent/homicidal ideation

Approach

- ask every patient: i.e. "Have you had any thoughts of wanting to harm or kill yourself?" or "With everything you've been going through, have you ever felt like you didn't want to be around anymore?"
- classify ideation
  - passive ideation ("death wish"): where patient would rather not be alive, but currently has no active plan for suicide
    - i.e. "I would rather not wake up" or "I would not mind if a car hit me"
  - active ideation
    - i.e. "I think about killing myself"
- assess risk
  - plan: "Do you have a plan as to how you would end your life?"
  - intent: "Do you think you would actually carry out this plan?" and "If not, why not?"
  - past attempts: number, lethality, outcome, medical intervention, while intoxicated?, precipitants
  - if intoxicated on the first approach, reassess when sober
- assess suicidal ideation
  - onset and frequency of thoughts: "When did this start?" or "How often do you have these thoughts?"
  - control over suicidal ideation: "How do you cope when you have these thoughts?" or "Could you call someone for help?"
  - intention: "Do you want to end your life?" or "Do you wish to kill yourself?"
  - intended lethality: "What do you think would happen if you actually took those pills?"
  - access to means: "How will you get a gun?" or "Which bridge do you think you would go to?"
  - time and place: "Have you picked a date and place?" or "Is it in an isolated location?"
  - provocative factors: "What makes you feel worse (i.e. being alone)?"
  - protective factors: "What keeps you alive (i.e. friends, family, pets, faith, therapist)?"
  - final arrangements: "Have you written a suicide note?" "Made a will? "Given away your belongings?"
  - practiced suicide or aborted attempts: "Have you ever put the gun to your head?" "Held the medications in your hand?" "Stood at the bridge?"
  - ambivalence: "I wonder if there is a part of you that wants to live, given that you came here for help?"
  - determine level of risk and develop treatment/safety plan

Suicidal Ideation Assessment

- Asking patients about suicide will not give them the idea or the incentive to die by suicide
- The best predictor of completed suicide is a history of attempted suicide
- The most common psychiatric disorders associated with completed suicide are mood disorders and alcohol use disorders

Suicide Risk Factors

SAD PERSONS
Sex (male)
Age >60 yr
Depression
Previous attempts
Ethanol abuse
Rational thinking loss (delusions, hallucinations, hopelessness)
Suicide in family
Organized plan
No spouse (no support systems)
Serious illness, intractable pain

Assessment of Suicide Attempt

- setting (isolated vs. others present/chance of discovery)
- planned vs. impulsive attempt, triggers/stressors
- substance use/intoxication
- medical attention (brought in by another person vs. brought in by self to ED)
- time lag from suicide attempt to ED arrival
- expectation of lethality, dying
- reaction to survival (guilt/remorse vs. disappointment/self-blame)
- evidence of escalation in potential lethal means

Epidemiology

- attempted:completed = 20:1 (100:1 in younger persons; 4:1 in older persons)
- M:F=1:4 for attempts, 3:1 for completed

Risk Factors

- epidemiologic factors
  - age: increases after age 14, second most common cause of death for ages 15-24, highest rates of completion in persons >75 yr
  - sex: male
  - race/ethnic background: White people or Indigenous peoples in Canada
  - marital status: widowed/divorced
  - living situation: alone; no children <18 y/o in the household
  - other: stressful life events, or access to firearms, or serious chronic disease
- psychiatric factors
  - past suicide attempt(s)
  - non-suicidal self-harm
  - eating disorders
  - bipolar disorder
  - major depression
  - mixed drug misuse
  - panic disorder
  - schizophrenia
  - personality disorders
  - alcohol use
  - trauma history
- psychosocial factors
  - recent, severe stressful life event (relationship, financial, trauma)
- psychiatric disorders
  - mood disorders (15% lifetime risk in depression; higher in bipolar disorder)
  - anxiety disorders (especially panic disorder)
  - schizophrenia (10-15% risk)
  - substance use disorder (especially alcohol – 15% lifetime risk)
  - eating disorders (5% lifetime risk)
  - adjustment disorder
  - conduct disorder
  - personality disorders (borderline, antisocial)
- past history
  - prior suicide attempt(s), most recent attempt
  - family history of suicide attempt/completion

Clinical Features

- symptoms associated with suicide:
  - hopelessness
  - anhedonia
  - insomnia
  - severe anxiety
  - impaired concentration
  - psychomotor agitation
  - dissociation

Management

- proper documentation of the clinical encounter and rationale for management is essential
- for higher risk patients (with a plan and intention to act, have access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder)
  - hospitalization should be strongly considered; assess decision-making capacity if patient demands to leave hospital
  - do not leave patient alone; remove potentially dangerous objects from room
  - if patient refuses to be hospitalized, complete form for involuntary admission (Form 1) and must give patient Form 30 to notify them of their admission (in Ontario)
- for lower risk patients (not actively suicidal, with no active plan, or access to lethal means)
  - discuss protective factors and supports in their life, remind them of what they live for, promote survival skills that helped them through previous suicide attempts
  - start managing underlying problems if suicide risk is not imminent (e.g., psychiatric disorders, psychosocial stressors)
  - make a safety plan that could include an agreement that they will:
    - not harm themselves
    - avoid alcohol, drugs, and situations that may trigger suicidal thoughts
    - follow-up with you at a designated time
    - contact a health care worker, call a crisis line, or go to an emergency department if they feel unsafe or if their suicidal feelings return or intensify
- patients with depression: consider hospitalization if symptoms are severe or if psychotic features are present; otherwise outpatient treatment with good supports and pharmacotherapy
- patients with alcohol- or substance-related issues: suicidality usually resolves with abstinence for a few days; if not, suspect depression
- patients with personality disorders: crisis intervention, may or may not hospitalize

- patients with schizophrenia/psychosis: hospitalization might be necessary if there are acute safety concerns
- patients with parasuicidal behaviours/self-mutilation: psychotherapy with brief crisis intervention when necessary, medications to treat underlying psychiatric condition if applicable

Psychotic Disorders

Definition

- characterized by a significant impairment in reality testing
- positive symptoms
  - delusions or hallucinations (with or without insight into their pathological nature)
  - grossly disorganized or abnormal motor behaviours (including catatonia)
  - formal thought disorder
- negative symptoms of schizophrenia
  - diminished emotional expression (i.e. affective flattening)
  - anhedonia
  - avolition
  - alogia
  - asociality

Differential Diagnosis of Psychosis

Approach

- differentiate among psychotic disorders and distinguish them from other primary diagnoses with psychotic features
- consider symptoms, persistence, and time
- symptoms: the primary diagnosis needs full criteria to be met
  - mood: depressive episodes with psychotic features, manic episodes with psychotic features
  - psychotic: consider symptoms in Criterion A of schizophrenia (see *Criteria for Schizophrenia, PS8*)
- persistence: is there a time when certain symptom clusters are present without other clusters?
  - i.e. if there is a period of time with mood symptoms, but not psychotic symptoms, consider mood disorder
  - i.e. if psychotic symptoms occur only with mood symptoms, consider mood disorder with psychotic features
  - i.e. if during a 2 wk period where psychotic symptoms persist in the absence of mood symptoms, consider schizoaffective disorder
  - i.e. if long periods with psychotic symptoms and brief or rare mood symptoms, consider schizophrenia
- time: how long have the symptoms been present?

Table 1. Differentiating Psychotic Disorders

Disorder	Psychotic Symptoms	Duration
Brief Psychotic Disorder	≥1 positive symptoms of Criterion A	<1 mo with eventual full return to premorbid functioning
Schizophreniform Disorder	Criterion A	1-6 mo
Schizophrenia	Criterion A	>6 mo
Schizoaffective Disorder	Criterion A + major mood episode (MDE or manic), ≥2 wk of psychotic symptoms without mood symptoms	>1 mo
Delusional Disorder	≥1 delusions (if hallucinations, related to delusional theme)	>1 mo
Substance-Induced Psychotic Disorder	Delusions or hallucinations	Onset during intoxication/withdrawal, resolve in <1 mo without use
2° to Mood Disorder	Mood symptoms dominant + delusions/ hallucinations (mood congruent)	Psychosis may be present only for the duration of the mood episode

Relevant Investigations

- CBC, electrolytes (including extended electrolytes), creatinine, glucose, urinalysis, urine drug screen, TSH, and vitamin B12
- LFTs, fasting lipids, HbA1C to obtain baseline levels prior to antipsychotic initiation
- optional: ECG (several antipsychotics affect cardiac conduction)
- if clinically indicated, order infectious work-up, inflammatory markers, and brain imaging

Delusions: fixed, false beliefs that are not amenable to change in light of conflicting evidence
Hallucinations: perceptual experiences occurring without an external stimulus

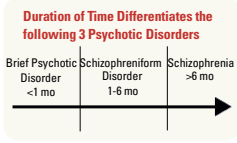

Figure 1. Differentiating psychotic disorders by duration

DDx for Psychosis
Primary psychotic disorders: schizophrenia, schizophreniform, brief psychotic, schizoaffective, delusional disorder
Mood disorders: MDD with psychotic features, bipolar disorder (manic or depressive episode with psychotic features)
Personality disorders: schizotypal, schizoid, borderline, paranoid, obsessive-compulsive (they predispose to psychosis, but presence of psychotic symptoms require another diagnosis)
General medical conditions: tumour, head trauma, dementia, delirium, metabolic, infection, stroke, temporal lobe epilepsy
Substance-induced psychosis: onset during intoxication or withdrawal, prescribed medications, toxins

Management of Acute Psychosis and Mania
- Ensure safety of self, patient, and other patients
- Have an exit strategy
- Decrease stimulation
- Assume a non-threatening stance
- IM medications (benzodiazepine and antipsychotic) often needed as patient may refuse oral medication
- Physical restraints may be necessary
- Do not use antidepressants or stimulants

Schizophrenia

DSM-5 DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA

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A. two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least one of these must be (1), (2), or (3)
   1. delusions
   2. hallucinations
   3. disorganized speech (e.g. frequent derailment or incoherence)
   4. grossly disorganized or catatonic behaviour
   5. negative symptoms (i.e. diminished emotional expression or avolition)

B. for a significant portion of time since the onset of the disturbance, level of functioning in one or more major areas (e.g. work, interpersonal relations, self-care) is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning)

C. continuous signs of the disturbance persist for at least 6 mo. This 6 mo period must include at least 1 mo of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences)

D. schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness

E. the disturbance is not attributable to the physiological effects of a substance (e.g. drug of abuse, medication) or another medical condition

F. if there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia are also present for at least 1 mo (or less if successfully treated)

- **specifiers**: type of episode (e.g. first episode, multiple episodes, continuous), in acute episode/partial/full remission, with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis

Epidemiology

- prevalence: 0.3-0.7%, M:F=1:1
- mean age of onset: females late-20s with a 2nd peak in mid-life; males early- to mid-20s (some cases with late onset)
- suicide risk: 5-6% die by suicide, 20% attempt suicide

Etiology

- multifactorial: disorder is a result of interaction between both biological and environmental factors
  - genetic: 40% concordance in monozygotic (MZ) twins; 46% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected; vulnerable genes include Disrupted-in-Schizophrenia 1 (DISC1); neuregulin 1 (NRG 1); dystrobrevin binding protein/dysbindin (DTNBP1); catechol-O-methyltransferase (COMT); d-amino acid oxidase activator (DAOA); metabotropic glutamate receptor 3 (GRM3); and brain-derived neurotrophic factor (BDNF)
  - neurochemistry ("dopamine hypothesis"): excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis, while decreased dopamine in the prefrontal cortex may mediate negative and cognitive symptoms. GABA, glutamate, and ACh dysfunction are also thought to be involved
  - neuroanatomy: decreased frontal lobe function; asymmetric temporal/limbic function; decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytoarchitectural abnormalities
  - neuroendocrinology: abnormal growth hormone, prolactin, cortisol, and ACTH
  - neuropsychology: global defects seen in attention, language, and memory suggest disrupted connectivity of neural networks
  - environmental: indirect evidence of cannabis use, geographical variance, winter season of birth, obstetrical complications, and prenatal viral exposure

Pathophysiology

- neurodegenerative theory: natural history may be a rapid or gradual decline in function and ability to communicate
  - glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
- neurodevelopmental theory: abnormal development of the brain from prenatal life
  - neurons fail to migrate correctly, make inappropriate connections, and undergo apoptosis in later life

Relationship Between Duration of Untreated Psychosis (DUP) and Outcome in First-Episode Schizophrenia
Am J Psychiatry 2005;162:1785-1804
Purpose: To review the association between DUP and symptom severity at first treatment contact, and between DUP and treatment outcomes.
Methods: Critical review and meta-analysis of studies involving patients with non-affective psychotic disorders at or close to first treatment.
Results: 43 studies with 4177 patients were included. Shorter DUP was associated with greater response to antipsychotic treatment, as measured by global psychopathology, positive symptoms, negative symptoms, and functional outcomes. At the time of treatment initiation, longer DUP was associated with the severity of negative symptoms but not with the severity of positive symptoms, global psychopathology, or neurocognitive function.
Conclusions: DUP may be a potentially modifiable prognostic factor.

Duration of Untreated Psychosis as Predictor of Long-term Outcome in Schizophrenia: Systematic Review and Meta-analysis
Brit J Psychiatry 2014;205:88-94
Purpose: To review the association between DUP and long-term outcomes of schizophrenia.
Methods: A systematic review and meta-analysis on the effects of duration of untreated psychosis on clinical, social, or quality of life outcomes at least 2 yr following psychosis in people with schizophrenia.
Results: 33 studies were included. Longer DUP was associated with poorer general symptomatic outcome, more severe positive and negative symptoms, lesser likelihood of remission, and poorer social functioning and global outcomes. Longer DUP was not associated with employment, quality of life, or hospital treatment.

Disorganized Behaviours in Schizophrenia
Catatonic stupor: fully conscious but mute, unresponsive, immobile, and maintaining bizarre positions for a long time
Catatonic excitement: uncontrolled and aimless motor activity, extreme agitation
Stereotypy: repeated but non-goal-directed movement (i.e. rocking)
Mannerisms: goal-directed activities that are odd or out of context (i.e. grimacing)
Echopraxia: imitates movements and gestures of others
Automatic obedience: carries out simple commands in robot-like fashion
Negativism: refuses to cooperate with simple requests for no apparent reason
Inappropriate affect, neglect of self-care, other odd behaviours (random shouting)

Comorbidity
- substance use disorders (>50% use tobacco)
- anxiety disorders
- reduced life expectancy secondary to medical comorbidities (i.e. obesity, diabetes, metabolic syndrome, cardiovascular/pulmonary disease)

Management of Schizophrenia
- biological/somatic
  - acute treatment and maintenance: antipsychotics (risperidone, aripiprazole, haloperidol, paliperidone; clozapine if resistant); regimens of IM q2-4 wk. Long-acting injectables (LAI or depot) shown to be more effective in reducing relapse and rehospitalization compared with oral alternatives
  - adjunctive: ± mood stabilizers (for aggression/impulsiveness - lithium, valproate, carbamazepine) ± anxiolytics ± ECT
  - maintenance treatment for at least 1-2 yr after the first episode, at least 5 yr after multiple episodes (relapse causes severe deterioration)
- psychosocial
  - psychotherapy (individual, family, group), supportive, CBT (see *Table 14, PS51*)
  - ACT (Assertive Community Treatment): mobile mental health teams that provide individualized treatment in the community and help patients with medication adherence, basic living skills, social support, job placements, resources
  - social skills training, employment programs, disability benefits
  - housing (group home, boarding home, transitional home)

Course and Prognosis
- majority of individuals display some type of prodromal phase
- course is variable: some individuals have exacerbations and remissions while others remain chronically ill; accurate prediction of the long-term outcome is not possible
- positive symptoms typically diminish with treatment; negative symptoms tend to be most persistent and cognitive symptoms may not improve
- over time: 1/3 improve, 1/3 remain the same, 1/3 worsen

Cannabis Use and Earlier Onset of Psychosis
Arch Gen Psychiatry 2011;68:555-561
Purpose: To examine the extent to which cannabis, alcohol, and other psychoactive drugs affect the age of onset of psychosis.
Method: A systematic review and meta-analysis. English studies were included that compared two cohorts: patients who used substances vs. patients who did not use substances.
Results: 83 studies were included. The age of onset in cannabis users was 2.7 yr younger than in nonusers. For broadly defined substance use, age of onset of psychosis was 2.0 yr earlier than for nonusers. Alcohol use was not associated with significantly earlier age of psychosis.
Conclusions: These results provide evidence that cannabis plays a role in earlier onset of psychosis.

Good Prognostic Factors
- Acute onset
- Later age of onset
- Shorter duration of prodrome
- Female gender
- Good cognitive functioning
- Good premorbid functioning
- No family history
- Presence of affective symptoms
- Absence of structural brain abnormalities
- Good response to drugs
- Good support system

Schizophreniform Disorder

Diagnosis
- criteria A, D, and E of schizophrenia are met; an episode of the disorder lasts for >1 mo but <6 mo
  - if the symptoms have extended past 6 mo the diagnosis becomes schizophrenia
  - specifiers: with/without good prognostic features (e.g. acute onset, confusion/perplexity, good premorbid functioning, absence of blunt/flat affect), with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis

Treatment
- similar to acute schizophrenia

Prognosis
- better than schizophrenia; 1/3 recover within 6 mo, 2/3 progress to schizophrenia

Brief Psychotic Disorder

Diagnosis
- criteria A1-A4, D, and E of schizophrenia are met; an episode lasts for at least 1 d, but less than 1 mo with eventual full return to premorbid level of functioning
- specifiers: with/without marked stressors, with postpartum onset, with catatonia, current severity
- can occur after a stressful event or postpartum (see *Postpartum Mood Disorders, PS14*)

Treatment
- secure/safe environment, antipsychotics, and anxiolytics

Prognosis
- good, self-limiting, should return to premorbid function within 1 mo

Schizoaffective Disorder

DSM-5 DIAGNOSTIC CRITERIA FOR SCHIZOAFFECTIVE DISORDER
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A. an uninterrupted period of illness during which there is a major mood episode concurrent with Criterion A of schizophrenia
B. delusions or hallucinations for 2 or more wk in the absence of a major mood episode during the lifetime duration of the illness

Non-bizarre delusions involve situations that could occur in real life (i.e. being followed, poisoned, loved at a distance) Bizarre delusions involve situations that cannot occur in real life (i.e. being kidnapped by aliens, having one's organs stolen)

C. symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual periods of the illness
D. the disturbance is not attributable to the effects of a substance or another medical condition
- **specifiers**: bipolar type, depressive type, with catatonia, type of episode (i.e. first episode, multiple episode), severity

Epidemiology
- one-third as prevalent as schizophrenia; schizoaffective disorder bipolar type more common in young adults, schizoaffective disorder depressive type more common in older adults
- depressive symptoms correlated with higher suicide risk (lifetime risk 5%)

Treatment
- antipsychotics, mood stabilizers, and antidepressants

Prognosis
- between that of schizophrenia and of mood disorder

Delusional Disorder

DSM-5 DIAGNOSTIC CRITERIA FOR DELUSIONAL DISORDER
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A. the presence of one (or more) delusions with a duration of 1 mo or longer
B. criterion A for schizophrenia has never been met
Note: hallucinations, if present, are not prominent and are related to the delusional theme
C. apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behaviour is not obviously bizarre or odd
D. if manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder
- **subtypes**: erotomanic, grandiose, jealous, persecutory, somatic, mixed, unspecified
- further specify: bizarre content, type of episode (e.g. first episode, multiple episode), severity

Treatment
- antipsychotics, psychotherapy, and antidepressants

Prognosis
- may respond well to antipsychotics, but most patients refuse them and have chronic, unremitting course; some maintain a high level of functioning; some progress to schizophrenia

Mood Disorders

Definitions
- accurate diagnosis of a mood disorder requires a careful past medical and psychiatric history to detect past mood episodes and to rule out whether these episodes were secondary to substance use, a medical condition, etc.
- mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration (i.e. major depressive, manic, mixed, hypomanic). DSM-5 Criteria for mood episodes are listed below
- types of mood disorders include:
  - depressive (MDD, persistent depressive disorder)
  - bipolar (bipolar I/II disorder, cyclothymia)
  - induced by or due to ("secondary to") a general medical condition (GMC), substance, medication, or other psychiatric condition

Medical Workup of Mood Disorder
- routine screening: physical exam, CBC, extended electrolytes, LFT, renal and thyroid function tests, drug screen, medications list
- additional screening: B12 (in older people), neurological consultation, chest x-ray, ECG, head imaging

Mood Episodes

DSM-5 DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE EPISODE (MDE)

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A. ≥5 of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia)

Note: Do not include symptoms that are clearly attributable to another medical condition

- depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
- markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- significant and unintentional weight loss/weight gain, or decrease/increase in appetite nearly every day
- insomnia or hypersomnia nearly every day
- psychomotor agitation or retardation nearly every day
- fatigue or loss of energy nearly every day
- feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- diminished ability to think or concentrate, or indecisiveness nearly every day
- recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. the episode is not attributable to the direct physiological effects of a substance or a GMC

Criteria for Depression (≥5)

MSIGECAPS
Mood: depressed
Sleep: increased/decreased
Interest: decreased
Guilt
Energy: decreased
Concentration: decreased
Appetite: increased/decreased
Psychomotor: agitation/retardation
Suicidal ideation

DSM-5 CRITERIA FOR MANIC EPISODE

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A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting ≥1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary)

B. during the period of mood disturbance and increased energy or activity, ≥3 of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behaviour

- inflated self-esteem or grandiosity
- decreased need for sleep (e.g. feels rested after only 3 h of sleep)
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
- increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained shopping sprees, sexual indiscretions, or foolish business investments)

C. the mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features

D. the episode is not attributable to the physiological effects of a substance or another medical condition

- Note: A full manic episode that emerges during antidepressant treatment but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis
- Note: Criteria A-D constitutes a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder

Criteria for Mania (≥3)

GST PAID
Grandiosity
Sleep (decreased need)
Talkative
Pleasurable activities, Painful consequences
Activity (increased)
Ideas (flight of)
Distractible

Hypomanic Episode

- criterion A and B of a manic episode is met, but duration is ≥4 d
- episode associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic and observable by others
- episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features (if these are present the episode is, by definition, manic)

Mixed Features

- episode specifier in a manic, hypomanic, or depressive episode of bipolar I or II (BDI/II) that indicates the presence of both depressive and manic symptoms concurrently, classified by the disorder and primary mood episode (i.e. BDI, current episode manic, with mixed features)
- clinical importance due to increased suicide risk and appropriate treatment
- if found in patient diagnosed with major depression, there is a high index of suspicion for BD
- while meeting the full criteria for a MDE, the patient has on most days ≥3 of criteria B for a manic episode
- while meeting the full criteria for a manic/hypomanic episode, the patient has on most days ≥3 of criteria A for a depressive episode (the following criterion A does not apply: psychomotor agitation, insomnia, difficulties concentrating, or weight changes)

Depressive Disorders

MAJOR DEPRESSIVE DISORDER

DSM-5 DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER (MDD)

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A. presence of a single MDE (vs. recurrent, which requires presence of two or more MDEs; to be considered separate episodes, there must be an interval of at least 2 consecutive mo in which criteria are not met for a MDE)
B. the MDE is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder NOS
C. there has never been a manic episode or a hypomanic episode

- Note: This exclusion does not apply if all of the manic-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of another medical condition
- **specifiers**: with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, seasonal pattern

Epidemiology

- Canadian annual/lifetime prevalence: 5%/11%
- peak prevalence age 15-25 yr (M:F=1:2)

Etiology

- biological
  - genetic: 65-75% MZ twins; 14-19% DZ twins; 2-4 fold increased risk in first-degree relatives
  - neurotransmitter dysfunction: decreased activity of 5-HT, NE, and DA at neuronal synapse; changes in GABA and glutamate; various changes detectable by fMRI
  - neuroendocrine dysfunction: abnormal HPA axis activity
  - neuroanatomy and neurophysiology: decreased hippocampal volume, increased size of ventricles; decreased REM latency and slow-wave sleep; increased REM length
  - immunologic: increased pro-inflammatory cytokines IL-6 and TNF
  - secondary to medical condition, medication, or substance use disorder
- psychosocial
  - cognitive (i.e. distorted schemata, Beck's cognitive triad: negative views of oneself, the world, and the future)
  - environmental factors (i.e. job loss, bereavement, history of abuse or neglect, early life adversity)
  - comorbid psychiatric diagnoses (i.e. anxiety, substance use disorder, developmental disability, dementia, eating disorders)

Risk Factors

- sex: F:M=2:1
- family history: depression, alcohol use disorder, suicide attempt or completion
- adverse childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
- personality: neurotic, insecure, dependent, obsessional
- recent stressors: illness, financial, legal, relational, academic
- lack of intimate, confiding relationships or social isolation
- low socioeconomic status

Clinically Significant Depressive Symptoms in the Elderly

- affects about 15% of community residents >65 y/o; up to 50% in nursing homes
- high suicide risk due to social isolation, chronic medical illness, and decreased independence
- suicide peaks: males ages 80-90, females ages 50-65
- low mood or dysphoria may not be a reliable indicator of depression in those >70 y/o
- often present with somatic complaints (i.e. changes in weight, sleep, energy; chronic pain) or anxiety symptoms
- may have prominent cognitive changes after onset of mood symptoms (dementia syndrome of depression)
- see *Table 3, PS26*, for a comparison of delirium and dementia

Treatment

- lifestyle: increased aerobic exercise, mindfulness-based stress reduction, sleep hygiene
- biological: SSRIs, SNRIs, other antidepressants, somatic therapies (see *Pharmacotherapy, PS50* and *Somatic Therapies, PS59)*
  - for MDD of moderate or greater severity, 1st line pharmacotherapy are used: most 2nd generation antidepressants, with escitalopram, mirtazapine, sertraline, venlafaxine, agomelatine, and citalopram showing evidence for superiority
  - for non or partial response, optimize the dose, switch to antidepressant with superiority, or add augmenting agent (i.e. aripiprazole, quetiapine, risperidone)
  - typical response to antidepressant treatment: physical symptoms improve at 2 wk, mood/cognition by 4 wk; if no improvement after 4 wk at the highest tolerated therapeutic dosage, alter regimen

Antidepressants for Depression in Physically Ill People
Cochrane DB Syst Rev 2010;CD007503
Purpose: To determine the efficacy of antidepressants in treating depression in people with comorbid physical illness.
Methods: Systematic review of RCTs comparing the efficacy of antidepressants vs. placebo in the treatment of major depression, adjustment disorder, and dysthymia in adults with comorbid depression and physical illness. Physical illness was defined as any medical condition known to have a biological underpinning where diagnosis is not purely symptom based.
Results: Fifty-one studies including 3603 participants were included in this review. Both tricyclic antidepressants and selective serotonin reuptake inhibitors were more effective than placebo at treating depression in adults with concurrent physical illness. Dry mouth and sexual dysfunction were more common in patients treated with an antidepressant.

See Landmark Psychiatry Trials table for more information on the STAR*D trial, which investigates the effectiveness of successive treatment steps of medication ± psychotherapy in adults with MDD.

- ECT: currently fastest and most effective treatment for MDD. Consider in severe, psychotic, or treatment-resistant cases
- rTMS: 1st line treatment for MDD for patients who have failed at least 1 antidepressant treatment. Efficacy equivalent to medications (but not to ECT) with good safety and tolerability
- phototherapy: especially if seasonal component, shift work, sleep dysregulation

• psychological
- individual therapy (CBT, interpersonal, behavioural activation, dynamic), group therapy, family therapy

• social: vocational rehabilitation, social skills training
• experimental: magnetic seizure therapy, deep brain stimulation, ketamine

Prognosis
• 1 yr after diagnosis of MDD without treatment: 40% of individuals will still have symptoms that are sufficiently severe to meet criteria for MDD, 20% will continue to have some symptoms that no longer meet criteria for MDD, 40% will have no symptoms

PERSISTENT DEPRESSIVE DISORDER

DSM-5 DIAGNOSTIC CRITERIA FOR PERSISTENT DEPRESSIVE DISORDER
Note: in DSM-IV-TR this was referred to as Dysthymic Disorder
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for ≥2 yr
Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr
B. presence, while depressed, of ≥2 of the following
- poor appetite or overeating
- insomnia or hypersomnia
- low energy or fatigue
- low self-esteem
- poor concentration or difficulty making decisions
- feelings of hopelessness

C. during the 2 yr period (1 yr for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 mo at a time
D. criteria for a major depressive disorder may be continuously present for 2 yr
E. there has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder
F. the disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder
G. the symptoms are not due to the direct physiological effects of a substance or another medical condition
H. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
• **specifiers:**
- with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, seasonal pattern
- partial remission, full remission
- early onset (<21 y/o), late onset (>21 y/o)
- with pure dysthymic syndrome (full criteria for MDE have not been met in at least preceding 2 yr), with persistent MDE (full criteria for MDE have been met throughout preceding 2 yr)
- with intermittent MDEs, with current episode: full criteria for a MDE are currently met, but there have been periods of at least 8 wk in at least the preceding 2 yr with symptoms below the threshold for a full MDE
- with intermittent MDEs, without current episode: full criteria for a MDE are not currently met, but there has been one or more MDEs in at least the preceding 2 yr
- specify current severity: mild, moderate, severe

Epidemiology
• lifetime prevalence: 2-3%; M=F

Treatment
• psychological
- traditionally, psychotherapy was the principal treatment for persistent depressive disorder; recent evidence suggests some (but generally inferior) benefit for pharmacological treatment. Combinations of the two may be most efficacious

• biological
- antidepressant therapy: SSRIs (e.g. sertraline, escitalopram), TCAs (e.g. nortriptyline)

See Landmark Psychiatry Trials table for more information on TRANSFORM-2, which details the use of esketamine nasal spray for patients with treatment-resistant depression.

Postpartum Mood Disorders

Postpartum "Blues"
- transient period of mild depression, mood instability, anxiety, decreased concentration; considered to be normal in response to fluctuating hormonal levels, the stress of childbirth, and the increased responsibilities of motherhood
- occurs in 50-80% of mothers; begins 2-4 d postpartum, usually lasts 48 h, can last up to 10 d
- does not require psychotropic medication
- usually mild or absent: feelings of inadequacy, anhedonia, thoughts of harming baby, suicidal thoughts

MAJOR DEPRESSIVE DISORDER WITH PERIPARTUM ONSET (POSTPARTUM DEPRESSION)

Clinical Features
- this specifier can apply to a MDE with onset during pregnancy or within 4 wk following delivery
- typically lasts 2-6 mo; residual symptoms can last up to 1 yr
- may present with psychosis (rare, 0.2% – more frequent with prior postpartum mood episodes and postpartum mania)
- severe symptoms may include complete disinterest in baby, suicidal and infanticidal ideation

Epidemiology
- occurs in up to 3-6% of mothers, up to 50% risk of recurrence

Risk Factors
- previous history of a mood disorder (postpartum or otherwise), family history of mood disorder
- psychosocial factors: stressful life events, unemployment, marital conflict, lack of social support, unwanted pregnancy, colicky or sick infant

Treatment
- psychotherapy (CBT or IPT)
- short-term safety of maternal SSRIs for breastfeeding infants established; long-term effects unknown
- if depression severe or psychotic symptoms present, consider ECT

Prognosis
- impact on child development: increased risk of cognitive delay, insecure attachment, behavioural disorders
- treatment of mother improves outcome for child at 8 mo through increased mother-child interaction

Bipolar Disorders

BIPOLAR I/BIPOLAR II DISORDER

Definition
- Bipolar I Disorder
  - disorder in which at least one manic episode has occurred
  - if manic symptoms lead to hospitalization, or if there are psychotic symptoms, the diagnosis is bipolar I
  - commonly accompanied by at least 1 MDE but not required for diagnosis
  - time spent in mood episodes: 53% asymptomatic, 32% depressed, 9% cycling/mixed, 6% hypo/manic
- Bipolar II Disorder
  - disorder in which there is at least 1 MDE, 1 hypomanic episode, and no manic episodes
  - while hypomania is less severe than mania, bipolar II is not a "milder" form of bipolar I
  - time spent in mood episodes: 46% asymptomatic, 50% depressed, 1% cycling/mixed, 2% hypo/manic
  - bipolar II is often missed due to the severity and chronicity of depressive episodes and low rates of spontaneous reporting and recognition of hypomanic episodes

Classification
- classification of BD involves describing the disorder (I or II) and the current or most recent mood episode as either manic, hypomanic, or depressed
- specifiers: with anxious distress, hypo/manic/depressed with mixed features, rapid cycling, melancholic features, atypical features, mood-congruent or -incongruent psychotic features, catatonia, peripartum onset, seasonal pattern, rapid cycling (≥4 mood episodes in 1 yr)

Epidemiology
- lifetime prevalence: 1% BD I, 1.1% BD II, 2.4% Subthreshold BD; M:F=1:1
- mean age of onset: 25 yr, usually MDE first, manic episode 6-10 yr after; average age of first manic episode: 32 yr
- 90% of those who have a single manic episode will have another

Selective Serotonin Reuptake Inhibitors or Serotonin-Norepinephrine Reuptake Inhibitors in Pregnancy: Infant and Childhood Outcomes
Paediatr Child Health 2021;26(5):321
Canadian Paediatric Society position statement: "While there are risks to taking medications during pregnancy, untreated or incompletely managed depression and anxiety also carry risks for the newborn. Poor neonatal adaptation syndrome (PNAS) occurs in one-third of newborns exposed to SSRIs or SNRIs in utero, and is generally mild and self-limiting. The low levels of SSRIs and SNRIs excreted in breast milk are compatible with breastfeeding. Persistent pulmonary hypertension of the newborn and congenital heart defects are rare associations of exposure to SSRIs or SNRIs in utero. There are inconsistencies in the literature regarding neurodevelopmental outcomes (specifically, ASD and ADHD). The inconsistencies likely relate to other factors (i.e. genetics, maternal depression, lifestyle, comorbidities), rather than exposure to SSRIs or SNRIs in utero. Health care providers and parents should be reassured that PNAS is generally treatable with non-pharmacological measures, and that the risk of serious adverse effects from exposure to SSRIs or SNRIs in utero is low."

Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects
JAMA Psychiatry 2020;77(12);1246-1255
Purpose: To determine which antidepressants used by pregnant women are associated with specific birth defects.
Methods: Case-control study of 30,630 mothers of infants with birth defects and 11,478 control mothers.
Results: Elevated adjusted odds ratios (aORs) were observed for SSRIs and congenital heart defects (CHD) (aOR 2.56, 95% CI 1.10 to 5.93) and SSRIs and non-CHD defects (aOR 5.11, 95% CI 1.29 to 20.24). The SSRI-CHD association was attenuated after partially accounting for maternal underlying conditions. Venlafaxine had elevated associations, with multiple defects that persisted after partially accounting for underlying conditions (aOR 9.14, 95% CI 1.91 to 43.83).
Conclusion: There are some associations between maternal antidepressant use and specific birth defects. Underlying conditions should be considered when assessing risk. Venlafaxine was associated with the highest number of defects.

Antidepressant Use in Pregnancy and the Risk of Cardiac Defects
NEJM 2014 Jun 19;370(25):2397-2407
Purpose: It is uncertain whether selective serotonin-reuptake inhibitors (SSRIs) and other antidepressants during pregnancy are associated with increased risk of congenital cardiac defects. There are concerns about an association between paroxetine use and right ventricular outflow tract obstruction, and between sertraline use and ventricular septal defects.
Methods: Cohort study including 949504 women enrolled in Medicaid for a 7 yr period. The risk of major cardiac defects among infants born to women who took antidepressants during the 1st trimester was compared with the risk among infants born to women who did not use antidepressants. An unadjusted analysis was used, possible confounders were considered.
Results: Overall, the chance of infants not exposed to antidepressants born with a cardiac defect was 72.3 per 10000 infants, and infants with exposure was 90.1 per 10000 infants. The relative risks of any cardiac defect with the use of SSRIs were 1.06 (95% CI, 0.93 to 1.22) in the fully adjusted analysis restricted to women with depression. No significant association was found between the use of paroxetine and right ventricular outflow tract obstruction (RR, 1.07) or between the use of sertraline and ventricular septal defects (RR, 1.04).
Conclusions: No substantial increase in risk of cardiac malformations attributable to antidepressant use during the 1st trimester.

Risk Factors
- genetic: 60-65% of bipolar patients have family history of a major mood disorder, especially bipolar disorder
- clinical features of MDE history favouring bipolar over unipolar diagnosis: early age of onset (<25 yr), increased number of MDEs, psychotic symptoms, postpartum onset, anxiety disorders (especially separation, panic), antidepressant failure due to early "poop out" or hypomanic symptoms, early impulsivity and aggression, substance misuse, cyclothymic temperament, family history of bipolar disorder, more suicide attempts, atypical depressive symptoms (hypersomnia, hyperphagia), psychomotor impairment

Treatment
- lifestyle: psychoeducation regarding cycling nature of illness, ensure regular check ins, develop early warning system, "emergency plan" for manic episodes, promote stable routine (sleep, meals, exercise)
- biological: lithium, anticonvulsants, antipsychotics, ECT (if resistant); monotherapy with antidepressants should be avoided
  - mood stabilizers vary in their ability to treat (reduce symptoms acutely) or stabilize (prevent relapse and recurrence) manic and depressive symptoms; multi-agent therapy is common
  - treating mania: lithium, divalproex, carbamazepine (2nd line), SGA, ECT (2nd line), benzodiazepines (for acute agitation)
  - preventing mania: same as above but usually at lower dosages, minus ECT and benzodiazepines
  - treating depression: lithium, lurasidone, quetiapine, lamotrigine, antidepressants (2nd line, only with mood stabilizer), ECT (2nd line)
  - preventing depression: same as above plus aripiprazole, divalproex (note: quetiapine is first line in treating bipolar II depression)
  - mixed episode or rapid cycling: multi-agent therapy: lithium or divalproex + SGA (lurasidone, aripiprazole)
  - check TSH if rapid cycling and treat hypothyroidism if found (hypothyroidism is a risk factor for rapid cycling)
  - psychological: supportive psychotherapy, CBT, IPT or interpersonal social rhythm therapy, family therapy
- social: vocational rehabilitation, consider leave of absence from school/work, assess capacity to manage finances, drug and EtOH cessation, sleep hygiene, social skills training, recruitment and education of family members

Course and Prognosis
- high suicide rate (15% mortality from suicide), especially depressive episodes in mixed states
- bipolar I and II disorder are chronic conditions with a relapsing and remitting course featuring alternating manic and depressive episodes; depressive symptoms tend to occur more frequently and last longer than manic symptoms
- can achieve high level of functioning between episodes
- may switch rapidly between depression and mania without any period of euthymia in between
- high recurrence rate for mania – 90% will have a subsequent episode in the next 5 yr
- long term follow-up of bipolar I – 15% well, 45% well with relapses, 30% partial remission, 10% chronically ill

CYCLOTHYMIA

Diagnosis
- presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for full hypomanic episode or MDE) for ≥2 yr; never without symptoms for >2 mo
- have never met criteria for MDE, manic, or hypomanic episodes
- symptoms are not due to the direct physiological effects of a substance or GMC
- symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Treatment
- similar to Bipolar I: mood stabilizer ± psychotherapy

Bipolar II is quite often missed and many patients are symptomatic for up to a decade before accurate diagnosis and treatment

Patients with bipolar disorder are at higher risk for suicide when they switch from mania to depression, especially as they become aware of consequences of their behaviour during the manic episode

Lithium is among few agents with proven efficacy in preventing suicide attempts and completions

Monotherapy with antidepressants should be avoided in patients with bipolar depression as patients can switch from depression into mania

The 4 L's for Bipolar Depression
Lithium, **L**amotrigine, **L**urasidone, Seroque**L**

A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-Term Change
J Clin Psychiatry 2006;67:277-86
Purpose: To evaluate long-term change with cognitive therapy plus emotive techniques for the treatment of bipolar disorder.
Methods: Blinded RCT including patients with DSM-IV bipolar I or II disorder allocated to either a 6 mo trial of cognitive therapy (CT) with emotive techniques or treatment as usual. Both groups received mood stabilizers. Main outcomes were relapse rates, dysfunctional attitudes, psychosocial functioning, hopelessness, self-control, and medication adherence. Patients were assessed by independent raters blinded to treatment group.
Results: At 6 mo, CT patients experienced fewer depressive symptoms and fewer dysfunctional attitudes. There was a non-significant (p=0.06) trend to greater time to depressive relapse. At 12 mo follow-up, CT patients had lower Young Mania Rating scores and improved behavioural self-control. At 18 mo, CT patients reported less severity of illness.
Conclusions: CT appears to provide benefits in the 12 mo after completion of therapy.

Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-analysis
JAMA Psychiatry 2020;78(2):141-150
Purpose: To determine which psychosocial interventions are associated with an improved course and medium-term outcomes in bipolar disorder.
Methods: Systematic review and meta-analysis of RCTs (n=39) that compared pharmacotherapy plus manualized psychotherapy, with pharmacotherapy plus a control intervention for patients with bipolar disorder.
Results: Manualized treatments were associated with lower recurrence rates than control treatments (OR 0.56, 95% CI 0.43 to 0.74).
Conclusions: Outpatients with bipolar disorder benefit from skills-based psychosocial interventions combined with pharmacotherapy.

Anxiety Disorders

Definitions

- fear is a universal human experience which can serve as an adaptive mechanism to facilitate appropriate reactions to external threat
- pathological fear is anxiety — this occurs when:
  - fear is greatly out of proportion to risk/severity of threat
  - response continues beyond existence of threat (prolonged, excessive, etc.) or becomes generalized to other similar or dissimilar situations
  - social or occupational functioning is impaired
- manifestations of anxiety are a result of the activation of the sympathetic nervous system and can be described through:
  - physiology: main brain structure involved is the amygdala; neurotransmitters involved include 5-HT, cholecystokinin, epinephrine, norepinephrine, and DA
  - psychology: one's thoughts about a given situation or stimulus contribute to the feeling of fear and perception of threat
  - behaviour: anxiety can lead to avoidance which can perpetuate the fear/avoidance

Differential Diagnosis

Table 2. Differential Diagnosis of Anxiety Disorders

Cardiovascular	Post-MI, arrhythmia, congestive heart failure, pulmonary embolus, mitral valve prolapse
Respiratory	Asthma, COPD, pneumonia
Endocrine	Hyperthyroidism, hypoglycemia, hyperadrenalism, hyperparathyroidism
Metabolic	Vitamin B12deficiency, folate deficiency, porphyria, hypoxemia, hypercalcemia
Neurologic	Neoplasm, vestibular dysfunction, encephalitis, trauma (contusion or hematoma), MS, temporal lobe epilepsy, migraine
Infectious	Cerebral (meningitis, HIV, syphilis) or systemic
GI	Gastritis, esophageal spasm
Substance-Induced	Intoxication (caffeine, cannabis, amphetamines, cocaine, thyroid replacement, OTC for colds/decongestants, steroids), withdrawal (benzodiazepines, alcohol)

Medical Workup of Anxiety Disorder

- only proceed with medical workup as clinically indicated
- recommended routine screening: vitals, physical exam, CBC, electrolytes, thyroid function test, glucose, ECG
- additional screening: extended electrolytes, vitamin B12, β-HCG, folate, chest x-ray, any other tests as per DDx in Table 2

Risk Factors for the Development of Anxiety Disorders

- biological
  - endocrine disorders (i.e. hyperthyroidism), respiratory conditions (i.e. asthma), CNS conditions (i.e. temporal lobe epilepsy), substances/medications (i.e. excessive stimulant use), chronic medical illness
  - personal or family history of anxiety or mood disorder
  - XX>XY chromosomes
- psychological, social
  - current stress, early childhood adversity or trauma, early parental loss, parental factors, socioeconomic status, temperament, behavioural inhibition

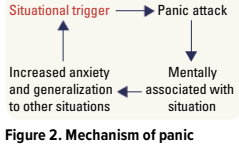

Figure 2. Mechanism of panic attacks

Panic Disorder

DSM-5 DIAGNOSTIC CRITERIA FOR PANIC DISORDER

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A. recurrent unexpected panic attacks; a panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur
   - palpitations, pounding heart, or accelerated heart rate
   - sweating
   - trembling or shaking
   - sensations of shortness of breath or smothering
   - feelings of choking
   - chest pain or discomfort
   - nausea or abdominal distress
   - feeling dizzy, unsteady, light-headed, or faint
   - chills or heat sensations
   - paresthesias (numbness or tingling sensations)
   - derealization (feelings of unreality) or depersonalization (being detached from oneself)
   - fear of losing control or "going crazy"
   - fear of dying

Criteria for Panic Attack (≥4)

STUDENTS FEAR the 3 Cs
Sweating
Trembling/shaking
Unsteadiness, dizziness
Depersonalization, Derealization
Excessive heart rate, palpitations
Nausea/abdominal distress
Tingling/numbness
Shortness of breath
Fear of dying, losing control, going crazy
3 Cs: Chest pain, **C**hills/hot flashes, **C**hoking

Duration typically 5-10 min

B. at least one of the attacks has been followed by 1 mo (or more) of one or both of the following:
- persistent concern or worry about additional panic attacks or their consequences
- a significant maladaptive change in behaviour related to the attacks

C. the disturbance is not attributable to the physiological effects of a substance or another medical condition
D. the disturbance is not better explained by another mental disorder

Epidemiology
- lifetime prevalence: 5% (one of the top five most common reasons to see a family physician); M:F=1:2-3
- onset: average early-mid 20s, familial pattern
- comorbidities: depression, agoraphobia, medical comorbidity

Treatment
- pharmacological and psychological treatment together can be very effective
- psychological
  - CBT: exposure (graduated exposure to unpleasant sensations of arousal associated with a panic attack for experiential disconfirmation of their fears), cognitive restructuring (addressing underlying beliefs regarding the panic attacks), relaxation techniques (visualization, box-breathing), psychoeducation
- pharmacological (first line agents)
  - SSRIs: fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine
  - SNRI: venlafaxine extended release
  - with SSRI/SNRIs, start with low doses and titrate up as tolerated
  - anxiety disorders often require treatment at higher doses for a longer period of time than depression (full response may take up to 12 wk)
  - treat for up to 1 yr after symptoms resolve to avoid relapse
  - explain expected adverse effects prior to initiation of therapy to prevent non-adherence
  - other antidepressants: (mirtazapine, TCAs)
  - benzodiazepines considered 2nd line (short-term, lowest effective dose, helpful while titrating antidepressant)

Prognosis
- 85% can achieve good results, 10-20% continue with significant symptoms. Longer term, 65% achieve remission
- clinical course: chronic, but episodic with psychosocial stressors

Panic Attack vs. Panic Disorder
Panic disorder requires recurrent, unexpected panic attacks + fear of another panic attack
Panic attacks can occur in the context of many different disorders

Starting Medication for Anxiety
Start low, go slow, aim high, and explain symptoms to expect prior to initiation of therapy to prevent non-adherence due to side effects

Agoraphobia

DSM-5 DIAGNOSTIC CRITERIA FOR AGORAPHOBIA

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. marked fear or anxiety about two (or more) of the following five situations:
- using public transportation
- being in open spaces
- being in enclosed places
- standing in line or being in a crowd
- being outside of the home alone

B. the individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms
C. the agoraphobic situations almost always provoke fear or anxiety
D. the agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety
E. the fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context
F. the fear, anxiety, or avoidance is persistent, typically lasting ≥6 mo
G. the fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
H. if another medical condition is present, the fear, anxiety, or avoidance is clearly excessive
I. the fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder and are not related exclusively to obsessions, perceived defects or flaws in physical appearance, reminders of traumatic events, or fear of separation

Note: agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned

Treatment
- current evidence suggests that treatment of agoraphobia should follow the same recommendations for agoraphobia treatment with panic disorder

Generalized Anxiety Disorder

DSM-5 DIAGNOSTIC CRITERIA FOR GENERALIZED ANXIETY DISORDER

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance)
B. the individual finds it difficult to control the worry
C. the anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 mo)
    1. restlessness or feeling keyed up or on edge
    2. being easily fatigued
    3. difficulty concentrating or mind going blank
    4. irritability
    5. muscle tension
    6. sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D. the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition
F. the disturbance is not better explained by another mental disorder

Criteria for GAD (≥3)

C-FIRST
Concentration issues
Fatigue
Irritability
Restlessness
Sleep disturbance
Tension (muscle)

Epidemiology

- 1 yr prevalence: 1-4%, lifetime prevalence 6%; M:F=1:2
    - 8% of all who seek primary care treatment (WHO)
    - in primary care: 70% initially present with physical symptoms as main concern
- bimodal age of onset: before 20 or middle adulthood

Source: Depression and other common mental disorders: Global health estimates. Geneva: World Health Organization, 2017.

Treatment

- lifestyle: avoid caffeine and EtOH, sleep hygiene
- psychological: CBT (cognitive restructuring), muscle relaxation techniques, mindfulness
- biological
    - 1st line: SSRIs (escitalopram, sertraline, paroxetine), SNRIs (venlafaxine XR, duloxetine), pregabalin
    - benzodiazepines considered 2nd line (short-term, lowest effective dose, helpful while titrating antidepressant)
    - β-blockers not recommended

Prognosis

- good with treatment
- depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress

Social Anxiety

Definition

- marked and persistent (>6 mo) fear of social or performance situations in which one is exposed to unfamiliar people or to possible scrutiny by others. They fear that they will be negatively evaluated in a way that may be humiliating, embarrassing, or lead to rejection (e.g. public speaking, initiating or maintaining conversation, dating, eating in public)
- situations are avoided or endured with intense anxiety and causes significant distress or impairment in functioning
- lifetime prevalence 8-12%; M:F ratio approximately equal

Epidemiology

- lifetime prevalence 8-12%; M:F ratio approximately equal

Treatment

- CBT, SSRIs and SNRIs; if poor response or intolerance: benzodiazepine, MAOI, pregabalin

Phobic Disorders

Specific Phobias

- definition: marked and persistent (>6 mo) fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
- lifetime prevalence 10-13%; M:F ratio variable
- types: animal/insect, environment (e.g. heights, storms), blood/injection/injury, situational (e.g. airplane, closed spaces), other (e.g. loud noise, clowns), multiple fears

Diagnostic Criteria for Phobic Disorders

- marked fear/anxiety about a specific object/situation
- exposure to stimulus almost invariably provokes an immediate fear/anxiety response; may present as a panic attack
- phobic object/situation is actively avoided or endured with intense anxiety

- fear/anxiety out of proportion to actual danger/sociocultural context and persistent (lasting 6 mo or more)
- person recognizes fear as excessive or unreasonable
- significant impact on daily routine, occupational/social functioning, and/or marked distress

Treatment
- psychological: psychoeducation, CBT (focusing on both in vivo and virtual exposure therapy, gradually facing feared situations)
- biological: minimal role for medications

Obsessive-Compulsive and Related Disorders

Obsessive-Compulsive Disorder

DSM-5 DIAGNOSTIC CRITERIA FOR OBSESSIVE-COMPULSIVE DISORDER
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. presence of obsessions, compulsions, or both
- obsessions are defined by (1) and (2)
  1. recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress
  2. the individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e. by performing a compulsion)
- compulsions are defined by (1) and (2)
  1. repetitive behaviours (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly
  2. the behaviours or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive

B. the obsessions or compulsions are time-consuming (e.g. take >1 h/d) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. the obsessive-compulsive symptoms are not attributable to the physiological effects

D. the disturbance is not better explained by the symptoms of another mental disorder

- **specifiers**: with good or fair insight, with poor insight, with absent insight/delusional beliefs, tic-related
- most common obsessions: contamination fear, pathological doubts, harm (sex, aggression), somatic dysfunctions, need for symmetry, religious
- most common compulsions: checking, washing, repeating, ordering, counting, need to ask, and hoarding
- rituals serve to counteract the anxiety induced by the obsessive thoughts

Epidemiology
- lifetime prevalence 3%
- mean age of onset: 20 yr; onset after 35 yr rare
- rate of OCD in first-degree relatives is higher than in the general population
- common comorbidities: anxiety disorders (>75%), depressive or bipolar disorder (>60%), obsessive-compulsive PD, tic disorders, substance use disorder, body dysmorphic disorder, trichotillomania, and excoriation disorder

Risk Factors
- etiology unknown but linked with:
  - neurological abnormalities: neurological dysfunction (brain injury, Sydenham's or Huntington's chorea), abnormal EEG, and abnormal evoked auditory potentials
  - family history of OCD or Tourette's disorder
  - pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) in children following group A β-streptococcal infection; also linked to D8/17 antigen positivity
  - social isolation, physical abuse, negative emotionality

Treatment
- CBT: ERP which involves exposure to feared situations using various techniques (e.g. imaginal exposure, systematic desensitization, flooding) with the addition of preventing the compulsive behaviours; cognitive strategies include challenging underlying beliefs
- pharmacotherapy: SSRIs (12-16 wk potential delay until response, higher therapeutic dosages than used for depression, benign side-effects), clomipramine; adjunctive antipsychotics (risperidone, aripiprazole) for refractory OCD
- neurosurgery or neurostimulation: anterior cingulotomy for severe refractory OCD, two techniques: radiofrequency thermolesion and gamma knife capsulotomy or cingulotomy (50-70% response rate); ECT (particularly for those with comorbid severe depression)

Prognosis
- may be refractory and chronic with waxing and waning symptoms (<20% remission rate without treatment)

Related Disorders

Body Dysmorphic Disorder
- preoccupation with ≥1 perceived flaws in physical appearance not observed by others
- repetitive behaviours (e.g. mirror checking, excessive grooming, skin picking, or reassurance seeking) or mental acts (e.g. comparing self to others) related to appearance
- ± muscle dysmorphia
- causes clinically significant distress or functional impairment
- rule out eating disorder
- mean age of onset: 15 y/o
- symptoms tend to be chronic; high rate of suicidal ideation and attempts; comorbidity with MDD, social anxiety disorder, and OCD
- treatment: SSRIs, CBT (specific to body dysmorphic disorder)

Hoarding Disorder
- persistent difficulty discarding possessions regardless of actual value
- feels the need to save items, discarding creates distress
- results in possessions cluttering/compromising active living areas (may be uncluttered with 3rd party intervention, i.e. family member, cleaners, authorities)
- causes clinically significant distress or functional impairment
- rule out brain injury, cerebrovascular disease, Prader-Willi syndrome, OCD, MDD (low energy), psychotic disorder (delusions), neurocognitive disorder, ASD (restricted interests)
- tends to begin in teens and worsens over time, more common in older populations, large genetic component
- treatment: CBT (specific to hoarding disorder)

Trichotillomania (Hair-Pulling Disorder)
- recurrent pulling out own hair resulting in hair loss (usually involves scalp, eyebrows, or eyelashes but may include other hair)
- repeated attempts to stop or decrease hair pulling
- causes clinically significant distress or functional impairment
- rule out dermatological condition, body dysmorphic disorder
- treatment: CBT (habit reversal training), SSRIs, 2nd gen. antipsychotics, N-acetylcysteine, or lithium

Excoriation (Skin-Picking) Disorder
- recurrent skin picking resulting in lesions
- repeated attempts to stop or decrease skin picking
- causes clinically significant distress or functional impairment
- rule out scabies, substance use (e.g. cocaine), psychotic disorder (e.g. delusions, tactile hallucinations), body dysmorphic disorder, stereotypic movement disorder, non-suicidal self-injury
- treatment similar to trichotillomania (described above)

Trauma- and Stressor-Related Disorders

Post-Traumatic Stress Disorder

DSM-5 DIAGNOSTIC CRITERIA FOR POST-TRAUMATIC STRESS DISORDER

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association.

A. exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
   1. directly experiencing the traumatic event(s)
   2. witnessing, in person, the event(s) as it occurred to others
   3. learning that the traumatic event(s) occurred to a close family member or close friend; in cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental
   4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g. first responders collecting human remains: police officers repeatedly exposed to details of child abuse)

B. presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)
   2. recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s)
   3. dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring
   4. intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
   5. marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)

The Trauma Triangle
The perpetrator
The victim
The rescuer

C. persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
    1. avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)
    2. avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)
D. negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
    1. inability to remember an important aspect of the traumatic event(s)
    2. persistent and exaggerated negative beliefs or expectations about oneself, others, or the world
    3. persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others
    4. persistent negative emotional state (e.g. fear, horror, anger, guilt, or shame)
    5. markedly diminished interest or participation in significant activities
    6. feelings of detachment or estrangement from others
    7. persistent inability to experience positive emotions
E. marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
    1. irritable behaviour and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects
    2. reckless or self-destructive behaviour
    3. hypervigilance
    4. exaggerated startle response
    5. problems with concentration
    6. sleep disturbance (e.g. difficulty falling or staying asleep or restless sleep)
F. duration of the disturbance (criteria B, C, D, and E) is more than 1 mo
G. the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
H. the disturbance is not attributable to the physiological effects of a substance or another medical condition

- **specifiers**:
    - with dissociative symptoms (not attributable to physiologic effects of a substance or a medical condition); this could involve either depersonalization (persistent or recurrent experiences of feeling detached from, or as if one were an outside observer of one's mental processes or body) or derealization (persistent or recurrent experiences of unreality of surroundings)
    - with delayed expression: the full diagnostic criteria are not met until 6 mo after the event

Criteria for Post-Traumatic Stress Disorder

TRAUMA
Traumatic event
Re-experience the event
Avoidance of stimuli associated with the trauma
Unable to function
More than a Month
Arousal increased
+ negative alterations in cognition and mood

Epidemiology

- lifetime prevalence in Canada is 9%; onset in mid-late 20s
- 75% have another comorbid psychiatric disorder; increased risk of suicide 2-3x
- high rates of chronic pain, sleep problems, sexual dysfunction, cognitive dysfunction
- prevalence F:M=2:1
- most common forms of trauma: unexpected death of someone close, sexual assault, serious illness or injury to someone close, physical assault by partner or caregiver
- risk factors: severity, duration, and proximity to trauma
- differential diagnosis: bipolar disorder, borderline personality disorder, acute stress disorder (3 d-1 mo after trauma)

Treatment

- trauma therapy, CBT
    - stage 1 - safety and stabilization: emotional regulation techniques (i.e. breathing, relaxation) to help build coping skills, medications for PTSD, manage substance use
    - stage 2 - remembrance and mourning: exposure to traumatic memories and work through distorted thoughts, relational patterns, and grief
    - stage 3 - reconnection and integration: exposure therapy, etc. create a new future, new relationships, strengthen identity
- early intervention via psychological support (not de-briefing)
- psychotherapy: CBT, DBT, supportive, eye movement desensitization and reprocessing (EMDR)
- biological
    - first line: fluoxetine, paroxetine, sertraline, venlafaxine XR (50-80% response with residual symptoms is common)
    - prazosin (for treating disturbing dreams and nightmares)
    - benzodiazepines (for acute anxiety; use with extreme caution)
    - adjunctive atypical antipsychotics (risperidone, olanzapine)

Psychological Therapies for Post-Traumatic Stress Disorder in Adults: Systematic Review and Meta-Analysis
Eur J Psychotraumatol 2020;11(1):1729633
Purpose: To determine the effect sizes of manualized therapies for PTSD.
Methods: Systematic review and meta-analysis of RCTs (n=114) that used any defined psychological therapy to reduce PTSD symptoms in comparison with a control group.
Results: There was robust evidence that trauma focused CBT, as well as Eye Movement Desensitization and Reprocessing (EMDR), had a clinically important effect.
Conclusion: Psychological therapies are recommended for PTSD. Trauma focused CBT and EMDR are recommended as first-line treatments.

Prognosis and Complications

- substance use disorder, relationship difficulties, depression, impaired social and occupational functioning disorders, personality disorders
- 50% of patients with PTSD have complete recovery within 3 mo, symptoms tend to diminish with age

Adjustment Disorder

Definition

- a diagnosis encompassing patients who have difficulty coping with a stressful life event or situation and develop acute, often transient, emotional or behavioural symptoms that resemble less severe versions of other psychiatric conditions

DSM-5 DIAGNOSTIC CRITERIA FOR ADJUSTMENT DISORDER

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A. the development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 mo of the onset of the stressor(s)
B. these symptoms or behaviours are clinically significant as evidenced by either of the following:
   - marked distress that is in excess of what would be expected from exposure to the stressor
   - significant impairment in social or occupational (academic) functioning
C. the stress-related disturbance does not meet criteria for another mental disorder and is not merely an exacerbation of a pre-existing mental disorder
D. the symptoms do not represent normal bereavement
E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 mo

- **specifiers**: with depressed mood, with anxiety, with mixed anxiety/depression, with conduct disturbance, with mixed disturbance of conduct/emotions, unspecified

Classification

- types of stressors
  - single (e.g. termination of romantic relationship)
  - multiple (e.g. marked business difficulties and marital problems)
  - recurrent (e.g. seasonal business crises)
  - continuous (e.g. living in a crime-ridden neighbourhood)
  - developmental events (e.g. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)

Epidemiology

- F:M=2:1, prevalence 2-8% of the population

Treatment

- brief psychotherapy: individual or group (particularly useful for patients dealing with unique and specific medical issues; e.g. colostomy or renal dialysis groups), crisis intervention
- biological: medications can be used to treat associated symptoms (insomnia, anxiety, or depression)
  - benzodiazepines may be used for those with significant anxiety symptoms (short-term, low-dose, regular schedule)

Acute Stress Disorder

May be a precursor to PTSD

Similar symptoms to PTSD

Symptoms persist for 3 d to 1 mo after exposure to a trauma

Bereavement

Clinical Features

- bereavement or grief is a reaction (involving thoughts, feelings, behaviours, and physiological responses) to significant loss, typically the death of a loved one; mourning is the process of integrating and adapting to the loss
- length and characteristics of "normal" bereavement vary between individual cultures
- normal response: protest → searching and acute anguish → despair and detachment → reorganization
- presence of the following symptoms may indicate abnormal grief/presence of MDD:
  - guilt about things other than actions taken or not taken by the survivor at the time of death
  - thoughts of death other than the survivor feeling that they would be better off dead or should have died with the deceased person; morbid preoccupation with worthlessness
  - marked psychomotor retardation; prolonged and marked functional impairment
  - hallucinatory experiences other than hearing the voice or transiently seeing the image of the deceased person
  - dysphoria that is pervasive and independent of thoughts or triggers of the deceased; absence of mood reactivity
- after 12 mo, if patient continues to yearn/long for the deceased, experience intense sorrow/emotional pain in response to the death, remain preoccupied with the deceased or with the circumstances of their death, then may start to consider a diagnosis of "persistent complex bereavement disorder"
- if a patient meets criteria for MDD, even in the context of a loss or bereavement scenario, they are still diagnosed with MDD

Treatment

- support and watchful waiting should be first line, as well as education and normalization of the grief process
- management should include assessment for secondary mental health or medical conditions such as PTSD, depression, suicidal ideation, increased substance use, and cardiovascular illnesses
- normal grief should not be treated with antidepressant or anti-anxiety medications as it is important to allow the person to experience the whole mourning process to achieve resolution

Risk Factors for Poor Bereavement Outcome

- Poor social supports
- Unanticipated death or lack of preparation for death
- Highly dependent relationship with deceased
- High initial distress
- Other concurrent stresses and losses
- Death of a child
- Pre-existing psychiatric disorders, especially depression and separation anxiety

Bereavement is associated with a significant increase in morbidity and mortality acutely following the loss, with effects seen up to 1 yr after

Loneliness is the most common symptom that continues to persist in normal bereavement and may last several years

- psychosocial: grief therapy (individual or group) is indicated for those needing additional support or experiencing complex grief/bereavement or significant MDD
- pharmacotherapy: if MDD present, past history of mood disorders, or severe symptoms

Neurocognitive Disorders

Delirium

- see Neurology, N21

DSM-5 DIAGNOSTIC CRITERIA FOR DELIRIUM

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. a disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (i.e. reduced orientation to the environment)
B. the disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
C. an additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)
D. the disturbances in criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal (e.g. coma)
E. there is evidence from the history, physical exam, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies

Clinical Features

- common symptoms
  - disturbance of attention: distractibility, disorientation (time, place, rarely person)
  - sleep/wake disturbance (daytime sedation, nighttime agitation, or wakefulness)
  - psychotic-like symptoms such as delusions, misinterpretations, illusions, and hallucinations (visual hallucinations are organic until proven otherwise)
  - affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
  - shifts in psychomotor activity (groping/picking at clothes, attempts to get out of bed when unsafe, sudden movements, sluggishness, lethargy)
- note: fluctuation/major changes in all of the above over the course of the day are to be expected - so collateral history is important
- hyperactive 30% vs. hypoactive 24% vs. mixed level of activity 46%

Risk Factors

- a wide range of medical conditions can precipitate delirium in a susceptible individual and there may be multiple underlying etiologies as a result
- polypharmacy particularly involving psychoactive drugs, anticholinergics, and serotonergic medications (e.g. Cogentin®, Benadryl®, benzodiazepines, opioids, and corticosteroids)
- infection, dehydration, malnutrition, immobility (including use of restraints), and use of bladder catheters
- hospitalization (incidence 10-56%); frail and surgical patients are at the greatest risk
- previous delirium
- nursing home residents (incidence 60%)
- old age (especially males)
- severe illness (e.g. cancer, AIDS)
- recent anesthesia or surgery (e.g. emergency hip fracture surgery, cardiac surgery)
- brain vulnerability: pre-existing neurologic or neurocognitive disorder, substance use disorder, past psychiatric illness

Assessment

- observation: for disturbances in consciousness, incoherent and/or disorganized speech, inability to concentrate upon conversation, disruption of sleep-wake cycle
- history: often gathered from collateral sources as patients may be confused and/or uncooperative
- clinical instruments: Confusion Assessment Method (CAM) and formal mental status testing, such as the Mini-Mental State Examination, used as needed, are helpful for baseline and ongoing assessment of altered mental state (i.e. score will improve as symptoms resolve)
- physical examination: may be difficult to perform; focus on vital signs, hydration status, potential infectious foci, unambiguous neurologic deficits, and suggestive features of general appearance (e.g. jaundice)
- medication review: drug toxicity accounts for approximately 30% of all delirium cases (including OTC, non-prescribed medications)

Confusion Assessment Method (CAM) for Diagnosis of Delirium

Highly sensitive and specific method to diagnose delirium
- Part 1: an assessment instrument that screens for overall cognitive impairment
- Part 2: includes four features found best able to distinguish delirium from other cognitive impairments

Need (1) + (2) + (3 or 4)
(1) Acute onset and fluctuating course
(2) Inattention
(3) Disorganized thinking
(4) Altered level of consciousness - hyperactive or hypoactive

Etiology of Delirium

I WATCH DEATH
Infectious (encephalitis, meningitis, urinary tract infection, pneumonia)
Withdrawal (alcohol, barbiturates, benzodiazepines)
Acute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
Trauma (head injury, postoperative)
CNS pathology (stroke, hemorrhage, tumour, seizure disorder, Parkinson's)
Hypoxia (anemia, cardiac failure, pulmonary embolus)
Deficiencies (vitamin B_{12}, folic acid, thiamine)
Endocrinopathies (thyroid, glucose, parathyroid, adrenal)
Acute vascular (shock, vasculitis, hypertensive encephalopathy)
Toxins: substance use, sedatives, opioids (especially morphine), anesthetics, anticholinergics, anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
Heavy metals (arsenic, lead, mercury)

Investigations
- standard bloodwork: CBC and differential, electrolytes (including Ca^{2+}, Mg^{2+}, and PO_4^{3-}), glucose, BUN, Cr, TSH/T4, LFTs, vitamin B_{12}, folate, albumin, toxicology screen; if indicated, order blood cultures and infectious serologies (HIV, VDRL, Hep B/C)
- standard imaging: CXR and CT head (indicated especially if focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, Hx of cancer); if indicated, abdominal x-ray for constipation and MRI head to detect or exclude subacute stroke and multifocal inflammatory lesions in patients with negative head CT
- standard urinalysis: urine dip; if indicated, urine drug screen, urine C&S
- if indicated: lumbar puncture and EEG (typical finding in delirium is generalized slowing, can also be used to rule out underlying seizures or post-ictal states as etiology)

Management
- goal is to treat the underlying causes of delirium while minimizing the physical and psychological distress to the patient
- step 1: identify and manage underlying cause
  - identify and treat underlying cause immediately
  - stop all non-essential medications
  - maintain nutrition, hydration, electrolyte balance, and monitor vitals
  - work to ensure regular bowel movements and skin care practices to prevent pressure ulcers
- step 2: optimize the environment
  - environment: quiet, well-lit, near window for cues regarding time of day
  - optimize hearing and vision; protect sleep (with medications if need be)
  - room near nursing station for closer observation; constant care if patient climbing out of bed, pulling out lines
  - family member present (or consider 1:1 sitter) for reassurance and re-orientation
  - frequent orientation: calendar, clock, reminders
  - avoid frequent changes of assigned nursing staff as well as room transfers
  - implement falls prevention strategies and enable safe mobility
  - physical restraints to maintain safety only if necessary; minimize lines and catheters
  - calm, supportive approach; therapeutic communication
- step 3: pharmacotherapy
  - low dose, high potency antipsychotics: haloperidol has the most evidence and can be given IV or IM; initiate Haldol® 0.5-1 mg IM/IV in elderly patients q1-2 h until agitation is under control for STAT or PRN situation; 0.5-2 mg PO q4-6 h - monitor for signs of EPS and QT prolongation
  - alternatives include risperidone, which is less sedating (0.25-0.5 mg PO BID; less sedating), olanzapine (more sedating, can be anticholinergic itself), quetiapine (if EPS sensitive but risk of hypotension; 6.25-50 mg PO qHS), aripiprazole (does not prolong QTc)
  - caution: all neuroleptics prolong the QT interval and decrease seizure threshold, thus increasing risk of cardiac arrhythmias and seizures, respectively; also, patients with Parkinson's disease or Lewy body dementia are particularly at high-risk of EPS
  - ECG to assess QT interval when considering treatment with an antipsychotic agent
  - benzodiazepines only used in alcohol/substance withdrawal delirium; otherwise, can worsen delirium (antipsychotics are not useful in EtOH or benzodiazepine withdrawal delirium); however, benzodiazepines should not be stopped if they are a long-standing medication or this may precipitate the delirium
  - try to minimize drugs with anticholinergic effects
  - note: antipsychotic medications are used in delirium to treat severe patient agitation, changing delirium from the hyperactive to hypoactive state; they do not treat the underlying "acute brain state" driving the delirium

Prognosis
- up to 50% 1 yr mortality rate after episode of delirium

Factors favouring psychosis over delirium
1. Auditory hallucinations that are structured and consistent
2. Personal or family history of psychosis
3. Gradual onset (unless substance induced)
4. History of a prodrome (insidious functional decline)

Factors favouring delirium over psychosis
1. Visual or tactile hallucinations
2. Acute onset
3. No previous history of psychosis
4. Sleep/wake changes
5. More global cognitive impairment
6. Recent medical illness/medication changes

Interventions for Preventing Delirium in Hospitalized Non-ICU Patients
Cochrane DB Syst Rev 2016:CD005563
Purpose: To assess effectiveness of interventions to prevent delirium in hospitalized patients in the non-ICU setting.
Methods: This study included RCTs on both pharmacological and non-pharmacological interventions for delirium in hospitalized patients in the non-ICU setting.
Results: 39 trials involving 16082 patients assessing 22 different interventions were included. Strong evidence was identified to support the use of multi-component interventions for the prevention of delirium. Multicomponent interventions include any intervention that uses non-pharmacological approaches to target multiple risk factors for delirium. Use of the Bispectral index to monitor anesthesia reduced incidence of postoperative delirium. Evidence to date does not support the use of cholinesterase inhibitors, antipsychotics, or melatonin to reduce incidence of delirium.

Major Neurocognitive Disorder (Dementia)

- see Neurology, N22

DSM-5 DIAGNOSTIC CRITERIA FOR MAJOR NEUROCOGNITIVE DISORDER
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on
   1. concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
   2. a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment

B. the cognitive deficits interfere with independence in everyday activities (i.e. at a minimum, requiring assistance with complex IADLs such as paying bills or managing medications)

C. the cognitive deficits do not occur exclusively in the context of a delirium

D. the cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia)
   - Note: if deficits do not interfere (as in B) and cognitive impairments are mild-moderate (as in A.2), this is considered "mild neurocognitive disorder;" see Neurology, N22

Specify whether due to:
- Alzheimer's disease
- frontotemporal lobar degeneration
- Lewy body disease
- vascular disease
- traumatic brain injury
- normal pressure hydrocephalus
- substance/medication use
- HIV infection
- Prion disease
- Parkinson's disease
- Huntington's disease
- another medical condition (e.g. nutritional deficiency)
- multiple etiologies
- unspecified
- also specify if mild, moderate or severe; major neurocognitive disorder diagnosis requires an impairment in functioning

Epidemiology
- prevalence increases with age: 5% in patients >65 yr, 35-50% in patients >85 yr
- probability of dementia in an older person with reported memory loss is estimated to be 60%
- prevalence is increased in people with Down's syndrome and head trauma
- Alzheimer's disease comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia neurocognitive disorder – see Neurology, N22)
- disease course: insidious onset, usually leading to death within 8-10 yr of first symptoms

Subtypes
- with or without behavioural disturbance (e.g. wandering, agitation)
- early-onset: <65 yr, late-onset: >65 yr

The 7 As of Dementia
Amnesia: loss of memory
Aphasia: loss of language ability
Apraxia: loss of ability to carry out purposeful movement
Agnosia: no longer recognizes things through the senses
Anosognosia: not knowing what one does not know
Apathy: loss of Initiative
Altered perception

Assessment and Investigations (to rule out reversible causes)
- history: consider the 7 A's of dementia, significant changes in ADLs and IADLs, medication compliance and substance use, risk factors for dementia and delirium, mood/anxiety and psychotic symptoms, screen for non-Alzheimer's dementias, assess safety and consent/capacity issues
- cognitive tests (e.g. MMSE, Rowland Universal Dementia Assessment Scale, Frontal Assessment Battery, MoCA)
- MoCA 18-25 suggestive of mild neurocognitive disorder (NCD), <18 suggestive of major NCD; beware of many false positives)
- standard "neurocognitive work-up": see *Delirium, PS23*
- as indicated: VDRL, HIV, LP, CXR, EEG, SPECT, head CT, or MRI
- indications for head imaging: same as for delirium, plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 mo), dementia of relatively short duration (<2 yr), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/seizures), bleeding disorder or use of anticoagulants, Hx of cancer, suspicions of normopressure hydrocephalus, and presence of unsuspected cerebrovascular disease would change management

The "Mini Cog" Rapid Assessment
3 word immediate recall
Clock drawn to "10 past 11"
3 word delayed recall

Management
- see Neurology, N22 for further management
- treat underlying medical problems and prevent new ones (e.g. treatment of hypertension and B12 deficiency)
- discontinue cognitively impairing medications (e.g. anticholinergic, benzodiazepines, non-benzodiazepine ("Z-drugs"))
- provide orientation cues for patient (e.g. clock, calendar)
- provide education and support for patient and family (e.g. day programs, respite care, support groups, home care)
- consider power of attorney/living will and long-term care plan (nursing home)
- inform Ministry of Transportation about patient's inability to drive safely
- consider pharmacological therapy
- to slow AD:
  - cholinesterase inhibitors (donepezil (Aricept®, 5-10 mg once daily), rivastigmine, galantamine) for mild to severe disease
  - NMDA receptor antagonist (memantine 5 mg once daily to 10 mg BID) for moderate to severe disease
- to manage AD:
  - low-dose atypical antipsychotics such as olanzapine (2.5-10 mg/d), quetiapine (25-200 mg/d), or risperidone (0.25-3 mg/d) for severe behavioural disturbances
  - trazodone (25-100 mg) can be used for night-time agitation
- to treat comorbid psychiatric conditions:
  - antidepressants such as escitalopram can be used for depressive episodes
  - "start low and go slow" (effective doses can be 1/3 to 1/2 that of regular adult age patients); reassess pharmacological therapy every 3 mo

Table 3. Comparison of Dementia, Delirium, and Cognitive Impairment Associated with Depression

	Dementia/Major Neurocognitive Disorder	Delirium	Cognitive Impairment Associated with Depression
Onset	Gradual/step-wise decline	Acute (usually hours to days)	Subacute
Duration	Months-years	Days-weeks	Variable
Natural History	Progressive Usually irreversible	Fluctuating, reversible, high morbidity/mortality in the elderly	Recurrent Partially reversible
Level of Consciousness	Normal	Fluctuating between hyperactive (agitation) and hypoactive (stupor) (over 24 h)	Normal
Attention	Not initially affected	Impaired (wandering, easy distraction)	Difficulty concentrating
Orientation	Intact initially	Impaired (usually to time and place), fluctuates	Intact
Behaviour	Disinhibition, impairment in ADL/IADL, personality change, loss of social graces	Potential for agitation/retardation (even severe)	Anhedonia, decreased/increased sleep/eating, agitation/retardation
Psychomotor	Normal	Fluctuates between extremes	Slowing or agitation
Sleep Wake Cycle	Fragmented sleep at night	Disturbed sleep wake cycle	Early morning awakening
Mood and Affect	Labile, anxiety or depression are common in the early stages	Anxious, irritable, fluctuating or apathetic, withdrawn	Depressed, pervasive
Cognition	Decreased executive functioning, paucity of thought	Fluctuating	May appear to be impaired/slowed
Memory Loss	Recent, eventually remote Typically, low insight	Marked recent	Recent More likely to complain
Language	Agnosia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia)	Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes	Not affected
Delusions	Compensatory	Nightmarish and poorly formed	Nihilistic, somatic
Hallucinations	Variable	Visual common	Less common; if present, auditory predominates
Quality of Hallucinations	Vacuous/bland	Frightening/bizarre	Self-deprecatory
Medical Status	Variable	Acute illness, drug toxicity	Rule out systemic illness, medications

Most Common Causes of Dementia

Alzheimer's disease (up to 50-60%): predominantly memory and learning issues, insidious onset/gradual progression
Frontotemporal degeneration (5%): language type (early preservation), behavioural type (apathy/disinhibition/self-neglect); more common among those with dementia that has onset before age 65; progressive
Lewy body disease (up to 25%): early changes in executive and attention, may fluctuate, well-formed visual hallucinations (e.g. rabbits), autonomic impairment (falls, hypotension), Parkinson's type EPS that does not respond well to pharmacotherapy and follows >1 yr after cognitive decline, fluctuating degree of cognitive impairment, sleep disturbances
Vascular disease (15-30%): vascular risk factors, focal neurological signs, abrupt onset, stepwise progression, executive dysfunction > memory impairment, personality and mood changes (loss of motivation)
Normal pressure hydrocephalus: abnormal gait ("magnetic gait"), early incontinence, rapidly progressive; dilated ventricles on imaging

Substance-Related and Addictive Disorders

Overview

- substance use disorder (SUD): a neurobiological disorder involving compulsive drug seeking and drug taking, despite adverse consequences, with loss of control over drug use (think issues with the "3 Cs": compulsive, consequences, control)
- it is possible to have a substance use disorder without physiological dependence (i.e. withdrawal syndrome or tolerance); dependence is the hallmark of substance use disorders and comes in the following forms:
  - behavioural: substance-seeking activities and pathological use patterns
  - physical: physiologic withdrawal effects without use or tolerance
  - cognitive: continuous or intermittent cravings for the substance to avoid dysphoria or to attain the desired effects of the substance
- drug misuse: drug use that deviates from the approved social or medical pattern, usually causing impairment or disruption to function in self or others
- these disorders are usually chronic with a relapsing and remitting course
- there are 10 separate classes of substances identified in the DSM-5: alcohol; caffeine; cannabis; hallucinogens (PCP or similarly acting arylcyclohexylamines and other hallucinogens); inhalants; opioids; sedatives, hypnotics, and anxiolytics (alcohol included); stimulants (amphetamine-type substances, cocaine, and other stimulants); tobacco; and other (or unknown) substances
- whereas substance use disorders imply addiction to substances, addictive disorders include process (behavioural) addictions such as gambling

Epidemiology

- the lifetime prevalence of SUD in Canada is 21.6% lifetime and 10.1% for the last 12 mo; for alcohol use disorder it is 18.1% and 3.2%; for cannabis use disorder 6.8% and 1.3%; and for other substances, 4.0% and 0.7%, respectively (data before the legalization of cannabis use in Canada)
- 47% of those with substance use disorder have mental health problems
- 29% of those with a mental health disorder have a substance use disorder
- 47% of those with schizophrenia and 25% of those with an anxiety disorder have a substance use disorder

Etiology

- almost all drugs (and activities) related to dependence directly or indirectly increase dopamine release from the ventral tegmental neurons synapsing onto the nucleus accumbens (known as the brain's 'reward pathway'), an action that contributes to their rewarding properties; with repeated use, they can modulate signaling pathways which further encourages their use, contributing to their addictive potential
- substance use disorders arise from multifactorial interactions between genetic (neurobiology), individual (psychological), and environmental factors (low socioeconomic status, peer influence, adverse childhood or traumatic experiences, social isolation, systemic racism, and chronic stress)
- certain comorbid conditions may also predispose individuals to a substance use disorder (e.g. mental illness, chronic disease, acute and chronic pain)
- environmental factors play a significant role in the exposure to the substance. For instance, the over prescription of opioids for pain in North America played a major role in the development of the opioid use disorder crisis

Diagnosis

- each specific substance is addressed as a separate use disorder and diagnosed utilizing the same overarching criteria (e.g. a single patient may have moderate alcohol use disorder, and a mild stimulant use disorder)
- testing for illicit drugs is most commonly done on urine or blood samples
  - serum toxicology screen measures recent alcohol consumption but has no relation to the diagnosis of alcohol use disorder
  - toxicology may be helpful in differentiating withdrawal from other mental disorders
  - urine drug screens are useful for detecting recent drug use, but not for diagnosing substance use disorders
- substance use disorders are measured on a continuum from mild to severe based on the number of criteria met within 12 mo
  - mild: 2-3
  - moderate: 4-5
  - severe: 6 or more
- criteria for substance use disorders (**PEC WITH MCAT**)
  - use despite **P**hysical or psychological problem (e.g. alcoholic liver disease or cocaine related nasal problems)
  - failure to fulfill **E**xternal roles at work/school/home
  - **C**raving or a strong desire to use substance
  - **W**ithdrawal
  - continued use despite **I**nterpersonal problems
  - **T**olerance: needing to use more substance to get same effect
  - use in physically **H**azardous situations
  - **M**ore substance used or for longer period than intended
  - unsuccessful attempts to **C**ut down
  - **A**ctivities given up due to substance
  - excessive **T**ime spent on using or finding substance

Table 4. Substance Symptomatology

	Drugs	Symptoms of Intoxication	Symptoms of Withdrawal
CNS Depressants	Alcohol, opioids, barbiturates, benzodiazepines, GHB	Euphoria, slurred speech, disinhibition, confusion, poor coordination, coma (severe)	Anxiety, anhedonia, tremor, seizures, insomnia, psychosis, delirium, death
Stimulants	Amphetamines, methylphenidate, MDMA, cocaine	Euphoria, mania, psychomotor agitation, anxiety, psychosis (especially paranoia), insomnia, cardiovascular complications (stroke, MI, arrhythmias), seizure	'Crash', craving, dysphoria, suicidality
Hallucinogens	LSD, mescaline, psilocybin, PCP, ketamine, ibogaine, salvia	Distortion of sensory stimuli and enhancement of feelings, psychosis (++ visual hallucinations), delirium, anxiety (panic), poor coordination	Usually absent

General Approach to Assessment

- a comprehensive evaluation should inquire about drug history including names of substances used, amount, frequency, duration, routes, last use, injection drug use, needle sharing, symptoms of withdrawal, consequences of use (medical, social, or personal), previous treatment programs and medical (e.g. HIV, hepatitis B and C, chronic pain), psychiatric (e.g. mood and anxiety disorders), and social history (e.g. family and housing arrangements, any child safety concerns)
- ask about more socially accepted substances (e.g. nicotine, alcohol) before asking about use of cannabis, misuse of prescription medicines, and about illicit drugs
- obtaining collateral history is recommended as well as evaluating patient insight into the problem

Questions to Characterize Substance Use and Risk Assessment (THE WATER)

When was the last **T**ime you used?

How long can you go without using?

Have you **E**xperienced medical or legal consequences of your use?

Any previous attempts to cut down or quit, and did you experience any **W**ithdrawal symptoms?

How has your substance use **A**ffected your work, school, relationships?

Are there any **T**riggers that you know will cause you to use?

Substances can be very **E**xpensive, how do you support your drug use?

By what **R**oute (oral ingestion, inhalation (snorting), smoking, IV) do you usually use?

Lab Testing
- urine, saliva, sweat, and hair can be tested for the presence of drugs
- urine is most commonly used due to ease of collection and adequate sensitivity and specificity, but it does not reflect serum concentrations
- proper urine drug testing involves an initial screening test (qualitative) followed by confirmatory testing for substances with positive screening results
- most confirmatory tests use gas or high-performance liquid chromatography
- post-ingestion window of detection with urine test: amphetamine (48 h), barbiturates (1-21 d), short-acting benzodiazepine (72 h), long-acting benzodiazepine (30 d), cocaine (12-72 h), morphine (48-72 h), methadone (72 h), oxycodone (2-4 d), PCP (8 d), cannabis (3 d for single use to >30 d for heavy users)
- limitations: negative tests cannot rule out substance use, and positive results cannot determine how much or frequency of use

General Approach to Treatment
- approach must be appropriate to the patient's current state of change (see Public Health and Preventive Medicine, *Health Promotion Strategies*, PH11)
- patients will change when the pain of change appears less than the pain of staying the same
- provider can help by providing psychoeducation (emphasize neurobiologic model of addiction), motivation, and hope
- principles of motivational interviewing (see *Psychotherapy, PS48*)
  - non-judgmental stance
  - space for patient to talk and reflect
  - offer accurate empathic reflections back to patient to help frame issue
- encourage and offer referral to evidence based services
  - social: 12-step programs (alcoholics anonymous, narcotics anonymous), family education, and support
  - psychological therapy: addiction counselling, MET, CBT, contingency management, group therapy, family therapy, marital counselling
  - medical management (differs depending on substance): acute detoxification, pharmacologic agents to aid maintenance. Ontario has the RAAM- Rapid Access to Addiction Medicine clinics that offer timely, low barrier, specialized services by self-referral
- harm reduction whenever possible: safe-sex practices, avoid driving while intoxicated, avoid substances with child care, safe needle practices/exchange, pill-testing kits, reducing tobacco use
- comorbid psychiatric conditions: many will resolve with successful treatment of the substance use disorder but patients who meet full criteria for another disorder should be treated for that disorder with psychological and pharmacologic therapies
- always consider duty to inform Ministry of Transportation for risk of driving or operating other vehicles

Nicotine

- see Family Medicine, FM13

Alcohol

- see Family Medicine, FM15 and Emergency Medicine, ER54

History
- Validated screening questionnaire for alcohol use disorders
  - **C** ever felt the need to **C**ut down on your drinking?
  - **A** ever felt **A**nnoyed at criticism of your drinking?
  - **G** ever feel **G**uilty about your drinking?
  - **E** ever need a drink first thing in the morning (**E**ye opener)?
    - for men, a score of ≥2 is a positive screen; for women, a score of ≥1 is a positive screen
    - if positive CAGE, then assess further to distinguish between problem drinking and alcohol use disorder

Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)

A "Standard Drink" (SD)
Spirit (40%): 1.5 oz. or 43 mL
Table Wine (12%): 5 oz. or 142 mL
Fortified Wine (18%): 3 oz. or 85 mL
Regular Beer (5%): 12 oz. or 341 mL
OR
1 pint of beer = 1.5 SD
1 bottle of wine = 5 SD
1 "mickey" = 8 SD (375 mL)
"26-er" = 17 SD (750 mL)
"40 oz." = 27 SD

Canada's Low-Risk Alcohol Drinking Guidelines

Moderate Drinking		
Men: 3 or less/d (≤15/wk)	Women: 2 or less/d (≤10/wk)	Elderly: 1 or less/d

Biochemical Markers of Prolonged Alcohol Use
- elevated liver function tests (AST, ALT, GGT), MCV, and carbohydrate-deficient transferrin (CDT)
- AST:ALT ratio >2:1 and elevated GGT are suggestive of alcohol use

Alcohol Intoxication

- throughout Canada, the legal limit for impaired driving is a BAC ≥0.08% (≥80 mg/dL or 17.4 mmol/L) which is typically reached after 4 drinks in women and 5 drinks in men in a 2 h period
- most signs of intoxication are present at over >21.7 mmol/L (100 mg/dL): altered perception, impaired judgement, ataxia, hyper-reflexia, impaired coordination, changes in mood/personality, prolonged reaction time, and slurred speech
- respiratory depression and arrest can occur with >60 mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)

Management of Alcohol Intoxication

- stabilize patient if there is reduced level of consciousness or vomiting; assess airways and respiratory function
- administer IV crystalloid fluids if evidence of volume depletion or shock; correct electrolytes and hypoglycemia
- monitor for signs of alcohol withdrawal following detoxification in patients with alcohol use disorder

Alcohol Withdrawal

- medical emergency: occurs within 12-48 h after prolonged heavy drinking and can be life-threatening
- ~50% of middle-class, functional individuals with alcohol use disorder have experienced alcohol withdrawal; 80% in hospitalized/homeless individuals
  - alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced:
    - stage 1 (onset 4-12 h after last drink): "the shakes", tremor, sweating, agitation, anorexia, cramps, diarrhea, sleep disturbance, anxiety, insomnia, headache. The majority of alcohol withdrawal presentations are mild to moderate (stage 1)
    - stage 2 (onset 12-24 h): alcoholic hallucinosis: visual, auditory, olfactory, or tactile hallucinations
    - stage 3 (onset 12-48 h): alcohol withdrawal seizures, usually tonic-clonic, non-focal, and brief (can occur as early as 2 h after alcohol consumption)
    - stage 4 (onset 48-96 h): delirium tremens, confusion/disorientation, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (diaphoresis, fever, tachycardia, HTN); this is a medical emergency
- course: almost completely reversible in young; elderly often left with cognitive deficits
- 20% mortality rate of severe presentations (delirium tremens) if untreated

Delirium Tremens (alcohol withdrawal delirium)

Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)
Hand tremor
Insomnia
Psychomotor agitation
Anxiety
Nausea or vomiting
Tonic-clonic seizures
Visual/tactile/auditory hallucinations
Persecutory delusions

See Landmark Clinical Trials table for more information on the COMBINE trial, which accesses combined pharmacotherapies and behavioural interventions for alcohol

Management of Alcohol Withdrawal

- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
  - areas of assessment include (**SHANT AS TAV**):
    - physical (5): paroxysmal **S**weats, **H**eadache/fullness in head, **A**gitation, **N**ausea and vomiting, **T**remor
    - psychological/cognitive (2): **A**nxiety, orientation/clouding of **S**ensorium
    - perceptual (3): **T**actile disturbances, **A**uditory disturbances, **V**isual disturbances
    - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67
    - mild <10, moderate 10-20, severe >20
- check for signs of hepatic failure (e.g. ascites, jaundice, and coagulopathy)

Table 5. CIWA-A Scale Treatment Protocol for Alcohol Withdrawal

Basic protocol	Diazepam 20 mg PO q1-2 h PRN until CIWA-A <10 points
	Observe 1-2 h after last dose and re-assess on CIWA-A scale
	Thiamine 100-250 mg IM then 100 mg PO once daily for 3 d, folic acid
	Supportive care (hydration, nutrition, and electrolyte replacement)
History of withdrawal seizures	Diazepam 20 mg PO q1 h for minimum of three doses regardless of subsequent CIWA scores
If age >65 or patient has severe liver disease, severe asthma or respiratory failure	Use a short acting benzodiazepine
	Lorazepam 1-4 mg PO/SL/IM q1-2 h
If hallucinations are present	Haloperidol 2-5 mg IM/PO q1-4 h – max 5 doses/d or atypical antipsychotics (olanzapine, risperidone)
	Diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold)
Admit to hospital if	Still in withdrawal after >80 mg of diazepam
	Delirium tremens, recurrent arrhythmias, or multiple seizures
	Medically ill or unsafe to discharge home

Wernicke-Korsakoff Syndrome

- alcohol-induced amnestic disorders due to thiamine deficiency (poor nutrition or malabsorption)
- necrotic lesions: mammillary bodies, thalamus, brainstem
- Wernicke's encephalopathy (acute and reversible): triad of oculomotor dysfunction such as nystagmus (CN VI palsy (eye pointing inwards)), gait ataxia, and confusion. If untreated, may progress to Korsakoff's syndrome
- Korsakoff's syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and compensatory confabulation (fabrication of imaginary experiences to compensate for memory loss); cannot occur only during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal

- management
  - Wernicke's preventative treatment (any patient in withdrawal): thiamine 100-250 mg IM/IV x 1 dose
  - Wernicke's acute treatment: thiamine 500 mg IV BID/TID x 72 h, then reassess
  - Korsakoff's: IV treatment as for Wernicke's followed by thiamine 100 mg PO TID x 3-12 mo

Treatment of Alcohol Use Disorder

- non-pharmacological
  - see *General Approach to Treatment, PS28*
- pharmacological
  - naltrexone (Revia®): opioid antagonist, shown to be successful in reducing the "high" associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges; can be started if still consuming alcohol or abstinent but can precipitate withdrawal in those with physical opioid dependence. Not safe in patients with acute liver failure, or opioid use in last 10 days.
  - acamprosate (Campral®): NMDA glutamate receptor antagonist; useful in maintaining abstinence and decreasing cravings. Not safe in patients with renal failure.
  - disulfiram (Antabuse®): prevents oxidation of alcohol (blocks acetaldehyde dehydrogenase) and causes an adverse reaction to alcohol (nausea/vomiting, tachycardia, shortness of breath, headache); if patient relapses, must wait 48 h before restarting Antabuse®; prescribed only when treatment goal is abstinence; RCT evidence is generally poor or negative due to poor medication adherence; contraindicated in severe renal disease, pregnancy, psychoses, and cardiac disease
  - some evidence for the use of gabapentin, topiramate, and ondansetron as anti-craving agents, but not approved by Health Canada approved for this indication (currently under investigation)

Opioids

- types of opioids: heroin, morphine, oxycodone, Tylenol #3® (codeine), hydromorphone, fentanyl, methadone, meperidine (Demerol®)
- in addition to working on opiate receptors, opiates also act on the dopaminergic system, which mediates their addictive properties
- most commonly used are: Percocet® (oxycodone/acetaminophen), Vicodin® (hydrocodone/acetaminophen), and OxyContin® (oxycodone)
- major risks associated with the use of contaminated needles: increased risk of hepatitis B and C, bacterial endocarditis, and HIV/AIDS
- recent considerations of inadvertent overdose secondary to contamination with fentanyl in the drug supply "opioid crisis" leading to 9000 deaths in Canada between January 2016 and June 2018

Acute Intoxication

- direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), pupil constriction (e.g. pinpoint pupils; exception is meperidine), and respiratory depression (can be fatal)
- medical emergency: typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
- management
  - ABCs
  - IV glucose
  - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
  - treatment: intubation and mechanical ventilation, ± naloxone drip, until patient alert without naloxone (up to >48 h with long-acting opioids)
- caution: opioids have a longer half-life than naloxone; may need to observe for toxic reaction for at least ≥24 h

Withdrawal

- symptoms: dysphoric mood, insomnia, drug-craving, myalgias, nausea or vomiting, yawning, chills, lacrimation, rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, fever; withdrawal symptoms can be severe but are not life threatening
- onset: 6-12 h (depending on half-life of opioid used); duration: 5-10 d
- complications: loss of tolerance (overdose on relapse), miscarriage, premature labour
- management: long-acting oral opioids (methadone, buprenorphine), α-adrenergic agonists (clonidine for symptomatic management of autonomic signs and symptoms of withdrawal)
- monitor withdrawal severity using Clinical Opioid Withdrawal Scale (COWS)

Treatment of Opioid Use Disorder

- see *General Approach to Treatment, PS28*
- long-term treatment may include maintenance treatment with methadone (opioid agonist) or buprenorphine (mixed agonist-antagonist)
- caution: methadone can cause QTc interval prolongation, screening ECG recommended

Opioid Antagonists
Naltrexone vs. Naloxone
Naltrexone (Revia®)
- Can be used for EtOH dependence (although not routinely used)
- Long half-life (>1 h)

Naloxone (Narcan®)
- Used for life-threatening CNS/ respiratory depression in opioid overdose
- Short half-life (<1 h)
- Very fast acting (min)
- High affinity for opioid receptor
- Induces opioid withdrawal symptoms

Maintenance Medication for Opiate Addiction: The Foundation of Recovery
J Addict Dis 2012;31:207-225
Maintenance treatment of opioid addiction with methadone or buprenorphine is associated with retention in treatment, reduction in illicit opiate use, decreased craving, and improved social function. Recently, studies showing extended release naltrexone injections have showed some promise.

Classic Opioid Overdose Triad (RAM)
Respiratory Depression
Altered Mental Status
Miosis

- Suboxone® formulation includes naloxone in addition to buprenorphine, in an effort to prevent injection of the drug. When naloxone is injected, it will precipitate opiate withdrawal and block the opiate effect of buprenorphine. However, it will not have this antagonist action when taken sublingually
- decreasing risk of overdose: patients with a history of opiate use, and/or friends, family members and co-workers working with people using opiates should be encouraged to carry a naloxone kit and educated on ways to limit overdose risk (i.e. use with a friend, avoid mixing drugs). It is a life-saving strategy

Common Presentations of Drug Use

System	Findings
General	Weight loss (especially with chronic use of cocaine, heroin) Injected conjunctiva (cannabis) Pinpoint pupils (opioids) Track marks (injection drugs)
MSK	Trauma
GI	Viral hepatitis (injection drugs) Unexplained elevations in ALT (injection drugs)
Behavioural	Missed appointments Non-compliance Drug-seeking (especially benzodiazepines, opioids)
Psychological	Insomnia Fatigue Depression Flat affect (benzodiazepines, barbiturates) Paranoia (cocaine) Psychosis (cocaine, cannabis, hallucinogens)
Social	Marital discord Family violence Work/school Absenteeism and poor performance

Cocaine

- street names: blow, C, coke, crack, flake, freebase, rock, snow
- alkaloid extracted from leaves of the coca plant; blocks presynaptic uptake of serotonin (causing euphoria), dopamine (linked to its addictive effect), norepinephrine and epinephrine (causing vasospasm, HTN)
- sodium channel blockade: cocaine slows or blocks nerve conduction and acts as a local anesthetic by altering recovery of neuronal Na^+ channels; it has a similar effect on cardiac Na^+ channels and in overdose can manifest on ECG as prolongation of the QRS complex
- self-administered by inhalation/smoking (crack) (90% bioavailability), insufflation (i.e. intranasal; 80% bioavailability), or intravenous route
- onset and duration of action: onset within seconds if inhaled or IV, lasting 15-30 min; onset in 3-5 min if insufflated, blood levels peak at 10-20 min with effects beginning to fade after 45-60 min; cocaine has a biologic half-life of 1 h, thus repeated self-administration is common among users to maintain an effect

Intoxication

- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (e.g. tachycardia, mydriasis, sweating, hypertension)
- prolonged use may result in paranoia and psychosis (including tactile hallucinations)

Overdose

- medical emergency: HTN, tachycardia, tonic-clonic seizures, dyspnea, hyperthermia, and ventricular arrhythmias
- the vasoconstrictive effects of cocaine can also result in stroke, MI, or intracranial hemorrhage
- treatment with IV diazepam to control seizures
- benzodiazepines may also be used for management of moderate agitation and anxiety, whereas severe agitation may require antipsychotics
- β-blockers (incl. labetalol or propranolol) are not recommended because risk of unopposed α-adrenergic stimulation can lead to coronary artery vasoconstriction and HTN

Withdrawal

- initial "crash" (1-48 h): increased sleep, increased appetite, dysphoria (non-life threatening)
- withdrawal (1-10 wk): dysphoric mood plus fatigue, irritability, vivid unpleasant dreams, insomnia or hypersomnia, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management

Treatment of Cocaine Use Disorder

- see *General Approach to Treatment, PS28*
- no pharmacologic agents have widespread evidence or acceptance of use (some evidence for off-label use of topiramate)
- referral to psychological interventions (e.g. relapse prevention) is the mainstay of long-term treatment

Complications

- cardiovascular: arrhythmias, MI, cerebrovascular accident, ruptured abdominal aortic aneurysm (AAA), chest pain (accounts for 40% of all cocaine-related ED visits)
- neurologic: seizures
- psychiatric: psychosis, delirium, suicidal ideation
- other: nasal septal deterioration, acute/chronic lung injury "crack lung," possible increased risk of connective tissue disease

Amphetamines

- includes prescription medications for ADHD (e.g. Ritalin® and Adderall®) and street drugs such as crystal meth
- intoxication characterized by euphoria, improved concentration, sympathetic and behavioural hyperactivity. At high doses, can mimic symptoms of psychosis or mania; can eventually cause coma
- chronic use can produce psychosis which can resemble schizophrenia with agitation, paranoia, delusions, and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- treatment of amphetamine induced psychosis: antipsychotics for acute presentation, benzodiazepines for agitation, β-blockers for tachycardia, HTN

Cannabis

- psychoactive substance: delta-9-tetrahydrocannabinol (Δ9-THC)
- general clinical manifestations: intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, altered sensorium, increased appetite, and muscle relaxation
- neuropsychiatric effects:
  - altered mood, perception, and thought content: increased sense of well-being, euphoria/laughter
  - impaired cognitive and psychomotor performance: reduced reaction time, impaired attention, concentration, and short-term memory. It may also impair motor coordination required to complete complex tasks requiring divided attention. Notably, psychomotor impairments may interfere with one's ability to operate heavy machinery such as automobiles
- inhaled cannabis: onset of psychoactive effects occurs rapidly with peak effects felt 15-30 min after intake and lasting up to 4 h
  - acute exacerbation in patients with asthma may be a complication with inhalation
- ingested cannabis: following oral ingestion, psychotropic effects set in with a delay of 30-90 min, reach their maximum after 2-3 h and last for about 4-12 h depending on dose
- high doses can cause depersonalization, paranoia, anxiety and may trigger psychosis and schizophrenia if predisposed
- chronic use is associated with tolerance and an apathetic, amotivational state; may also exacerbate respiratory problems such as asthma and chronic bronchitis
- assessment: standard urine drug screens
- treatment of cannabis use disorder: see *General Approach to Treatment, PS28*
- cessation following heavy use produces a significant withdrawal syndrome: irritability, anxiety, insomnia, decreased food intake

Hallucinogens

- types of hallucinogens by primary action
  - 5-HT2A agonists: lysergic acid diethylamide (LSD), mescaline (peyote), psilocybin mushrooms, N,N-Dimethyltryptamine (DMT) (ayahuasca)
  - NMDA antagonists: phencyclidine (PCP), ketamine
  - κ-opioid agonists: salvia divinorum, ibogaine
- 5-HT2A agonists are most commonly used; intoxication characterized by tachycardia, HTN, mydriasis, tremor, hyperpyrexia, and a variety of perceptual, mood and cognitive changes (rarely, if ever, deadly; treat vitals symptomatically)
- psychological effects of high doses: depersonalization, derealization, paranoia, and anxiety (panic with agoraphobia)
- tolerance develops rapidly (hours-days) to most hallucinogens; physical dependence is not thought to occur, although psychological dependence and harmful use patterns can still occur
- no specific withdrawal syndrome characterized but may experience "flashbacks" (i.e. a recurrence of symptoms after acute intoxication has worn off; may occur months to years after last use)
- management of acute intoxication: support, reassurance, diminished stimulation; benzodiazepines (e.g. lorazepam) or high potency antipsychotics (e.g. haloperidol) seldom required (if used, use small doses), minimize use of restraints
- long term adverse effects: controversial role in triggering psychiatric disorders, particularly mood or psychosis, thought to be chiefly in individuals with genetic or other risk factors
- Hallucinogen Persisting Perception Disorder: DSM-5 diagnosis characterized by long lasting, spontaneous, intermittent, distressing recurrences of visual perceptual changes reminiscent of those experienced with hallucinogen exposure

Cannabinoid Hyperemesis Syndrome
An interesting and relatively new clinical phenomenon associated with chronic cannabis use characterized by cyclical, recurrent severe nausea, vomiting, and colicky pain. Possibly due to increased potency of available THC products. Patients often present to ED in acute distress with no evidence of specific GI pathology. Many patients will successfully self-medicate with hot baths or showers

Evidence Based Medical Uses of Cannabis
Chemotherapy-induced nausea and vomiting
Spasticity, muscle spasms (multiple sclerosis, spinal cord injury)
Chronic pain (neuropathic pain)

Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: a Systematic Review
Lancet 2007;370:319-28
Purpose: To review the evidence for cannabis use and occurrence of psychotic or affective mental health outcomes.
Study Characteristics: A meta-analysis of 35 population-based longitudinal studies, or case-control studies nested within longitudinal designs.
Results: There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted OR=1.41, 95% CI=1.20-1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently (2.09, 95% CI=1.54-2.84). Findings for depression, suicidal thoughts, and anxiety outcomes were less consistent. In both cases (psychotic and affective outcomes), a substantial confounding effect was present.
Conclusions: The findings are consistent with the view that cannabis increases risk of psychotic outcomes independent of transient intoxication effects, although evidence is less strong for affective outcomes. Although cannabis use and the development of psychosis are strongly associated, it is difficult to determine causality and it is possible that the association results from confounding factors or bias. The authors did conclude that there is sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

Cannabis Use and Psychosis: a Review of Reviews
Eur Arch Psychiatry Clin Neurosci 2019;10.1007/s00406-019-01068-z
Purpose: To review the evidence on cannabis use and the development of psychosis
Methods: This study included systematic reviews and meta-analyses published after 2006. Studies on cannabis use and psychosis were included regardless of use pattern (lifetime, past year, past month, daily use, intensive use, occasional use) and type of psychosis (acute psychosis, psychotic disorders, schizophrenia).
Results: 26 systematic reviews and meta-analyses met inclusion criteria. A dose dependent relationship was identified between cannabis use and the development of psychotic illness. Cannabis users also had earlier symptom onset, increased relapse rate, more hospitalization, and more positive symptoms compared to non-users.

"Club Drugs"

Table 6. The Mechanism and Effects of Common "Club Drugs"

Drug	Mechanism	Effect	Adverse Effects
MDMA ("Ecstasy", "X", "E", "M", "Molly")	Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and stimulant	Enhanced sensorium; feelings of well-being, empathy	Diaphoresis, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, hyperthermia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death
Gamma Hydroxybutyrate (GHB, "G", "Liquid Ecstasy")	Biphasic dopamine response (inhibition then release) and releases opiate-like substance	Euphoric effects, increased aggression, impaired judgment	Diaphoresis, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia Severe withdrawal from abrupt cessation of high doses results in tremor, seizures, psychosis
Flunitrazepam (Rohypnol®, "Roofies", "Rope", "The Forget Pill")	Potent benzodiazepine, rapid oral absorption	Sedation, psychomotor impairment, amnestic effects, decreased sexual inhibition	CNS depression with EtOH
Ketamine ("Special K", "Kit-Kat")	NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics and by veterinarians	"Dissociative" state, profound amnesia/analgesia, hallucinations and sympathomimetic effects	Psychological distress, accidents due to intensity of experience and lack of bodily control In overdose: decreased LOC, respiratory depression, catatonia
Methamphetamine ("speed", "meth", "chalk", "ice", "crystal")	Amphetamine stimulant, induces norepinephrine, dopamine, and serotonin release	Rush begins in min, effects last 6-8 h, increased activity, decreased appetite, general sense of well-being, tolerance occurs quickly, users often binge and crash	Short-term use: high agitation, rage, violent behaviour, occasionally hyperthermia and convulsions Long-term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (especially formication), delusions, mood disturbance, suicidal and homicidal thoughts, stroke May be contaminated with lead, and IV users may present with acute lead poisoning
Phencyclidine ("PCP", "angel dust")	Not understood, used by veterinarians to immobilize large animals	Amnestic, euphoric, hallucinatory state	Horizontal/vertical nystagmus, myoclonus, ataxia, autonomic instability (treat with diazepam IV), prolonged agitated psychosis (treat with haloperidol) High-risk for suicide; violence towards others High dose can cause coma

Date Rape Drugs
Gamma-hydroxybutyrate (GHB)
Flunitrazepam (Rohypnol®)
Ketamine (sometimes used as it is tasteless and odourless)

Formication
Tactile hallucination that insects or snakes are crawling over or under the skin (especially associated with crystal meth use but also observed among some cocaine and PCP users)

Emerging Medical Uses of Hallucinogens
Many hallucinogens are currently under investigation for therapeutic benefit; LSD & psilocybin for end of life anxiety, MDMA for PTSD, ketamine for rapid treatment of depression, ibogaine derivatives for addiction

Somatic Symptom and Related Disorders

General Characteristics

- physical signs and symptoms that lack objective medical support and emerge in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance (suffering is out of keeping with what would be normally expected)
- cause significant distress or impairment in functioning
- symptoms are produced unconsciously and are not the result of malingering or factitious disorder, which are disorders of voluntary presentation, or intentionally inducing symptoms for secondary gain
- primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict with no external incentive
- secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (e.g. work)
- theories for root cause: may represent a masked presentation of a psychiatric issue; amplified perception; social/cultural norms that devalue psychological suffering; lack of ability/language to express distress in a non-somatic way

Management of Somatic Symptom and Related Disorders

- brief, regularly scheduled visits with GP to facilitate therapeutic relationship and help patient feel supported (e.g. q4-6 wk)
- limit number of physicians involved in care, minimize medical investigations, coordinate necessary investigations, and enable collaborative communication among all involved care providers
- emphasis on mechanism of the symptoms and not on the cause, while focusing on what the patient can change and control; the psychosocial coping skills, not their physical symptoms (functional recovery > explanation of symptoms)
- focus on functional improvement (physiotherapy, occupational therapy) and provide psychoeducation to validate suffering in the face of medically unexplained symptoms
- psychotherapy: CBT, psychodynamic therapy, mindfulness interventions, biofeedback
- minimize psychotropic drugs: anxiolytics for short-term use only (associated with worse outcomes), antidepressants for comorbid depression and anxiety

Malingering: intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by secondary gain/external reward (e.g. avoiding work, obtaining financial compensation, or obtaining drugs)

Factitious Disorder: intentional production or feigning of physical or psychological signs or symptoms. Unlike malingering, patients are not motivated by secondary gain but rather may seek sympathy, nurturance, and attention

Somatic Symptom Disorder

DSM-5 DIAGNOSTIC CRITERIA FOR SOMATIC SYMPTOM DISORDER

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A. one or more somatic symptoms that are distressing or result in significant disruption of daily life
B. excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
    1. disproportionate and persistent thoughts about the seriousness of one's symptoms
    2. persistently high level of anxiety about health or symptoms
    3. excessive time and energy devoted to these symptoms or health concerns
C. although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 mo)

- **somatic symptom disorder with predominant pain** (previously pain disorder) for those whose somatic symptom is primarily pain
- patients experience physical symptoms, and believe these symptoms represent the manifestation of a serious illness and engage in repeated behaviours (such as checking for bodily abnormalities and seeking medical reassurance)
- persistent belief despite negative medical investigations and may develop different symptoms over time
- lifetime prevalence may be around 5-7% in the general adult population
- females tend to report more somatic symptoms than males do; cultural factors may influence sex ratio
- other risk factors include: history of sexual abuse, lower education and socioeconomic status, and concurrent psychiatric/chronic physical illnesses
- complications: anxiety and depression commonly comorbid (up to 80%), unnecessary medications, or surgery
- often a misdiagnosis for an insidious illness, so rule out all organic illnesses (e.g. multiple sclerosis)
- DDx: GAD, depressive disorder, delusional disorder, body dysmorphic disorder, obsessive compulsive disorder, other medical condition

Illness Anxiety Disorder

- preoccupation with fear of having, or the idea that one has a serious disease to the point of causing significant impairment
- convictions persist despite negative investigations and medical reassurance; however, able to acknowledge the possibility that feared disease is not present, unlike a delusion, which is a fixed belief
- somatic symptoms are mild or not present (not acute)
- there is a high level of anxiety about health and the individual is easily alarmed about personal health status
- person engages in maladaptive behaviour such as excessive physical checking or total healthcare avoidance
- duration is ≥6 mo; onset in 3rd-4th decade of life
- epidemiology: 3-5% of patients seen by primary care physicians; increased risk of substance use problems
- possible role for SSRIs as treatment due to generally high level of anxiety
- specifiers: care-seeking type or care-avoidant type

Conversion Disorder (Functional Neurological Symptom Disorder)

- one or more symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or GMC (e.g. impaired coordination, local paralysis, double vision, seizures, or convulsions)
- does not need to be preceded by a psychological event as per previous DSM criteria; however this is still worth exploring as many patients will present after such an event, or are related to a medical diagnosis in a first-degree relative
- incidence of 2-5 in 100000 in general population; up to 20-25% of neurology inpatients and 5% of psychiatry inpatients
- more common in rural populations and in individuals with limited medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 mo)
- incompatible findings detected from specific neurological testing can help differentiate between functional and neurological origin (e.g. Hoover's sign and dermatome testing)
- for more details about Conversion Disorder, please consult the DSM-5

Screening questions for somatic disorders

1. When did the symptoms start?
2. Have you been frustrated with getting no answers?
3. What has been your experience with other physicians?
4. What is your understanding of your symptoms?
5. How have the symptoms affected your life?

Table 7. Differential of Somatic Symptom and Related Disorders

	Somatic Symptom Disorder	Illness Anxiety Disorder	Conversion Disorder	Factitious Disorder	Malingering
Somatic Symptoms	Present	Mild or absent	Neurologic, voluntary motor or sensory	Psychological or physical	Psychological or physical
Symptoms Produced	Unconsciously	Unconsciously	Unconsciously	Consciously	Consciously
Physical Findings	Absent	Absent	Incompatible	Possible, attempts to falsify	Possible, attempts to falsify

La belle indifference: an inappropriately cavalier patient attitude in the face of serious symptoms; classically associated with conversion disorder but is not diagnostic

Hoover's sign: involuntary extension of the "normal" leg occurs when flexing the contralateral leg against resistance

Dissociative Disorders

General Characteristics

- severe dissociation resulting in breakdown of integrated functions of consciousness and perception of self
- severe stress or traumas are predisposing factors for dissociative disorders (e.g. survivors of significant or chronic trauma, child abuse)
- result in significant distress or impairment in social/occupational functioning
- psychotherapy (psychodynamic, CBT) are the mainstays of treatment; lack of evidence for use of medications
- DDx: PTSD, acute stress disorder, borderline personality disorder, somatic symptom disorder, substance use disorder, GMC (various neurologic disorders including complex/partial seizures, migraine, Cotard syndrome)

Dissociative Identity Disorder

- disruption of identity characterized by ≥2 distinct personality states or an experience of possession
- can manifest as sudden alterations in sense of self and agency (ego-dystonic emotions, behaviours, speech)
- features recurrent episodes of amnesia (declarative or procedural) as well as episodes of depersonalization and derealization
- rare (<1%); can manifest at any age, although childhood physical/sexual abuse or neglect are a major risk factor
- caution: high-risk of attempting suicide and/or self-harm
- DDx includes borderline personality disorder and PTSD

Dissociative Amnesia

- inability to recall important autobiographical information, usually of a traumatic or stressful nature, that is inconsistent with normal forgetting and not attributable to a psychiatric disorder, a medical illness, or effects of a substance
- localized/selective amnesia: failure to recall all/some events during a prescribed period of time (however procedural memory is preserved)
- can experience periods of flashbacks or nightmares related to associated trauma, increased risk of suicide as amnesia resolves
- generalized amnesia (more rare): complete loss of memory for one's life history, ± procedural knowledge, ± semantic knowledge; usually sudden onset; often presents with perplexity, disorientation, and aimless wandering

Dissociative Fugue
Sudden unexpected travel away from home that is accompanied by amnesia for identity or other autobiographical details

Depersonalization/Derealization Disorder

- persistent or recurrent episodes of one or both of:
  - depersonalization: experiences of detachment from oneself, feelings of unreality, or a sense of being an outside observer to one's thoughts, feelings, speech, and actions (can feature distortions in perception including time, as well as emotional and physical numbing)
  - derealization: experiences of unreality or detachment with respect to the surroundings (i.e. feeling as if in a dream, or that the world is not real; external visual world is foggy or distorted)
- transient (s-h) experiences of this nature are quite common in the general population
- episodes can range from h-yr; patients are often quite distressed and verbalize concerns of "going crazy"

During depersonalization (detachment from one's self) or derealization (detachment from one's surroundings), patients usually have intact reality testing, which adds to their alarming nature

Sleep Disorders

- for more information regarding normal sleep cycles and the illnesses described, see Neurology, *Sleep Disorders*, N48

Overview

- adequate sleep is essential to normal functioning; deprivation can lead to cognitive impairment and increased mortality
- circadian rhythms help regulate mood and cognitive performance
- neurotransmitters commonly implicated in psychiatric illnesses also regulate sleep
  - increased ACh activity and decreased activity of monoamine neurotransmitters are associated with greater REM sleep
  - decreased adrenergic and cholinergic activity are associated with NREM sleep
- depression is associated with decreased Δ (deep, slow-wave) sleep, decreased REM latency, and increased REM density
- criteria for sleep disorders:
  - must cause significant distress or impairment in normal functioning
  - not due to a General Medical Condition (GMC) or medications/drugs (unless specified)

Management

- sleep hygiene is a simple, effective, but often underutilized method for addressing sleep disturbances; recommendations include:
  - waking up and going to bed at same time every day, including on weekends
  - avoiding long periods of wakefulness in bed
  - not using bed for non-sleep activities (reading, TV, work)
  - avoiding screens, especially smartphones and iPads in the hour before bed
  - avoiding napping
  - discontinuing or reducing consumption of alcohol, caffeine, drugs
  - exercising at least 3-4x/wk (but not in the evening if this interferes with sleep)
- cognitive behavioural therapy for insomnia (CBTi) is considered first-line treatment for chronic insomnia
- pharmacological treatments are illness-specific
  - avoid benzodiazepines: increased risk of abuse/dependence, rebound anxiety/insomnia, cognitive impairment, daytime somnolence, and disturbed sleep architecture (suppresses deep and REM sleep)
  - non-benzodiazepines (e.g. zopiclone/eszopiclone/zolpidem, lemborexant, low dose doxepin) are preferred and effective for short-term treatment; they should be re-evaluated regularly as long-term use is associated with dependency
  - "z-drugs": common side-effect is bitter metallic taste, which is improved by something acidic such as orange juice; high doses increase risk of cognitive impairment and falls (particularly among the elderly)
  - lemborexant (orexin receptor antagonist) reduces wake pressure/drive, as opposed to increasing sleep pressure/drive with other sedating agents; avoid use in patients with narcolepsy or cataplexy
  - trazodone, mirtazapine, and quetiapine can be prescribed off-label if there are comorbid psychiatric symptoms
  - low-dose amitriptyline can be prescribed for patients with comorbid pain
  - screen for complex sleep behaviours before and after prescribing a medication for insomnia
  - consider whether sleep issue is part of another psychiatric or medical illness and treat those conditions

Table 8. Major DSM-5 Sleep-Wake Disorders

Note: For more information regarding specific disorders, see Neurology, *Sleep Disorders*, N48; Family Medicine, *Sleep Disorders*, FM49 and Respirology, *Sleep Apnea*, R29

Category	Disorder	Description	Management
Dyssomnias (insufficient, excessive, or altered timing of sleep)	**Insomnia disorder**	Difficulty initiating/maintaining sleep or early-morning awakening with inability to return to sleep; can be acute or chronic (≥3 mo)	Sleep hygiene measures CBT for insomnia Non-benzodiazepines are first-line ("z-drugs", lemborexant, low dose doxepin)
	Hypersomnolence disorder	Excessive daytime sleepiness despite sleeping at least 7 h; difficulty being fully awake after awakening at least 3 times per wk for at least 3 mo	Modafinil or stimulant drugs Scheduled napping
	Narcolepsy	Classic tetrad consists of recurrent attacks of irrepressible need to sleep (sleep attacks), REM-related sleep phenomena, hypnagogic or hypnopompic hallucinations, and cataplexy (sudden loss of tone evoked by strong emotion without LOC)	Sleep hygiene Amphetamines (methamphetamine) Non-amphetamines (Modafinil, sodium oxybate)
	Circadian rhythm sleep-wake disorders	Insomnia or excessive sleepiness due to misalignment or alteration in endogenous circadian rhythm	Melatonin Bright light phototherapy Modafinil if severe
	Restless legs syndrome	Uncomfortable, frequent urge to move legs at night; relief with movement and aggravation with inactivity	Dopamine agonists and benzodiazepines are first-line Replace iron if low ferritin Modify medications that may be exacerbating symptoms
	Substance/medication-induced sleep disorder	Disturbance in sleep (insomnia or daytime sleepiness) caused by substance/medication intoxication or withdrawal	
Breathing-Related Sleep Disorders	**Obstructive sleep apnea hypopnea**	Breathing issues due to repetitive collapse of the upper airway during sleep - resulting in nonrestorative sleep and excessive daytime sleepiness; snoring, disrupted sleep, and morning headaches are common signs	Continuous positive airway pressure (CPAP) Weight loss/exercise Surgery
	Central sleep apnea	Breathing issues due to aberrant brain signaling More common among chronic opioid users	CPAP/bilevel positive airway pressure (BiPAP) Supplemental oxygen
	Sleep-related hypoventilation	Breathing issues due to decreased responsiveness to carbon dioxide levels (decreased respiration)	CPAP/BiPAP Medications that support breathing
Parasomnias (unusual sleep-related behaviours)	**Non-rapid eye movement sleep arousal disorders**	Incomplete awakening from sleep, complex motor behaviour without conscious awareness; amnesia regarding episodes; includes symptoms of:	
		Sleepwalking: rising from bed and walking about, blank face, unresponsive, awakened with difficulty	Most cases do not require treatment aside from addressing precipitating factors and education regarding sleep hygiene Severe cases may respond to low-dose clonazepam
		Sleep terrors: recurrent episodes of abrupt terror arousals from sleep, usually beginning with a panicky scream, intense fear, and autonomic arousal; relative unresponsiveness to comfort during episodes	Often self-limited and benign
		Specifiers: sleep-related sexual behaviour (sexsomnia) and sleep-related eating	
	Nightmare disorder	Repeated extended, extremely dysphoric, often very vivid, well-remembered dreams that usually involve significant threats; rapid orientation and alertness on awakening with autonomic arousal	Reassurance Desensitization/imagery rehearsal therapy Prazosin can be helpful for those with PTSD
	Rapid eye movement sleep behaviour disorder	Arousal during sleep, associated with vocalization and/or complex motor behaviours; can cause violent injuries; rapid orientation and alertness on awakening	Melatonin Clonazepam Discontinuation of causative medications such as TCAs, SSRIs, and SNRIs

Sexuality and Gender

- Cis refers to a person whose gender identity or expression aligns with their sex assigned at birth
- Trans refers to a person whose gender identity or expression differs from their sex assigned at birth

Gender Dysphoria

Definition
- discomfort or distress caused by a discrepancy between sex assigned at birth and a person's gender identity
- gender identity refers to a person's intrinsic sense of self as male, female, both, neither, or anywhere along the spectrum
- for more details about Gender Dysphoria, please consult the DSM-5

Clinical Features
- a marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
- a strong desire to alter, or have taken measures to alter, their primary and secondary sexual characteristics (or in young adolescents, a desire to prevent their development), and adopt the behaviours of their experienced gender

Management
- supportive psychotherapy or other mental health counselling
- hormone therapy with feminizing (e.g. estrogen and anti-androgen) or masculinizing (e.g. testosterone) agents
- gender affirming surgery (e.g. "top" surgery: breast augmentation, chest reconstruction; "bottom" surgery: vaginoplasty, hysterectomy, metoidoplasty, clitoral release, and phalloplasty)
- refer to social and institutional supports (e.g. peer support groups, community organizations, providing documentation to support changes in name and gender on identity documents)

Providing Gender-Affirming Care
There is an increased burden of poor mental health outcomes among trans and gender-diverse individuals. Many factors contribute to this, including transphobia, violence, and barriers accessing affirming primary or specialist care. Additionally, internal stressors, such as expectations of rejection and concealment of sexual orientation, may lead to negative mental health outcomes.

Gender-affirming care involves determining an individual's unique needs and supporting them in a way that respects their gender identity. Practitioners should strive to provide gender-affirming care, beginning with familiarizing themselves with the language their patients would like to be used (e.g. What pronouns do you use? How would you describe your gender identity?). It is also important for practitioners to recognize that patients are their own experts in their experiences and may be experiencing gender euphoria (i.e., the feeling of satisfaction or joy with the congruence between one's gender identity and gender expression), even before seeking medical intervention.

Paraphilic Disorders

Definition
- intense and persistent sexual arousal over a period of at least 6 mo that is elicited by something other than genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners
- paraphilic disorder: when paraphilia causes distress or functional impairment to the individual, or a paraphilia whose realization entails personal harm or risk of harming others

Clinical Features
- begins in childhood or early adolescence; increasing complexity and stability with age
- tends to be chronic but decreases in intensity with advancing age; may increase with stress
- rarely self-referred; come to medical attention through interpersonal or legal conflict
- person usually has more than one paraphilia; more common in men (only 5% of patients with paraphilia are women)
- subtypes:
  - voyeuristic - sexual arousal when spying intentionally on unsuspecting individuals
  - exhibitionistic - sexual arousal from the act or fantasy of exposing one's genitals to non-consenting individuals
  - frotteuristic - sexual arousal from touching or rubbing one's genitals up against non-consenting individuals
  - sexual masochism - sexual arousal from being humiliated, beaten, bound, or otherwise made to suffer
  - sexual sadism - sexual arousal from the psychological or physical suffering of a victim including humiliation
  - pedophilic - sexual attraction to prepubescent children - may be exclusive (only children) or nonexclusive (children and adults)
  - fetishistic - recurrent, intense sexual arousal from an inanimate object or specific focus on a non-genital body part(s)
  - transvestic - sexual arousal from act or fantasies of cross-dressing
  - other specified paraphilic disorder or unspecified paraphilic disorder

Management
- anti-androgen drugs (e.g. medroxyprogesterone or leuprolide)
- SSRIs (e.g. high-dose fluoxetine)
- behaviour modification
- psychotherapy

Sexual Addiction

- definition: engaging in persistent and escalating patterns of sexual behaviour, despite increasing negative consequences to self and others
- clinical features: may be characterized by compulsive searching for multiple sexual partners, persistent thoughts of or craving for sex to the detriment of other activities, compulsive masturbation, extensive use of pornography, compulsive sexuality in a relationship, and feelings of remorse or guilt after sex
- management: CBT, 12-step programs, SSRIs to reduce libido

Sexual Dysfunction

- important to identify treatable causes (e.g. atrophic vaginitis, diabetes, antidepressant medications)
- see Gynecology, GY34 and Urology, U33

Eating Disorders

Definition
- eating disorders are characterized by a persistent disturbance of eating that impairs psychosocial functioning or health
- disorders include: anorexia nervosa, avoidant/restrictive food intake disorder, binge eating disorder, bulimia nervosa, pica, and rumination disorder

Epidemiology
- anorexia nervosa (AN): 1% of adolescent and young adult females; 0.3% males; onset in mid-teens (14-18 yr)
- bulimia nervosa (BN): 2-4% of adolescent and young adult females; 0.5% males; onset in late teens or early adulthood
- F:M=10:1; mortality of AN 5-10%
- common comorbidities: depression (50-75%), substance misuse (35% in BN, 15% in AN), OCD (25% in AN)

Etiology
- multifactorial: psychological, sociological, and biological associations
- individual: perfectionism, lack of control in other life areas, history of sexual abuse
- personality: anxiety, perfectionism, obsessionality, negative emotionality, cognitive inflexibility
- family & sociocultural: invalidating family structure, prevalent in industrialized societies, idealization of thinness in the media, athletic demands
- puberty
- genetic factors
  - AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs vs. concordance in 1 of 14 dizygotic pairs (10x greater risk among first-degree relatives)
  - BN: higher familial incidence of affective disorders than the general population

Risk Factors
- physical factors: obesity, chronic medical illness (e.g. DM)
- psychological factors: individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance use disorder), history of sexual abuse (especially for BN), competitive athletes, concurrent associated mental illness (depression, OCD, anxiety disorder (especially panic and agoraphobia), substance use disorder (specifically for BN))

Complications
- growth delay, osteoporosis (40%), osteopenia (50%), cardiovascular complications (bradycardia, QTc prolongation, starvation edema), gastrointestinal complications (irritable bowel syndrome, constipation, gastric dilation), electrolyte disturbances (hypokalemia, hypomagnesemia, hypophosphatemia), refeeding syndrome, and endocrine abnormalities (increased GH, reduced LH, FSH, and T3)

Eating Disorder Screening
Method to identify patients with eating disorders. A "Yes" to two or more questions is associated with a sensitivity and specificity of 78 and 88%, respectively

SCOFF
Do you make yourself **S**ick because you feel uncomfortably full?
Do you worry you have lost **C**ontrol over how much you eat?
Have you recently lost more than **O**ne stone (14 pounds or 6.35 kg) in a 3 mo period?
Do you believe yourself to be **F**at when others say you are too thin?
Would you say that **F**ood dominates your life?

Anorexia Nervosa

DSM-5 DIAGNOSTIC CRITERIA FOR ANOREXIA NERVOSA
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A. restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected
B. intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though at a significantly low weight

Athletic Triad
Disordered eating
Amenorrhea
Osteoporosis

Some patients with insulin-dependent DM may stop their insulin in order to lose weight

C. disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight
- **specifiers**: partial remission, full remission, severity based on BMI (mild = BMI >17 kg/m^2, moderate = BMI 16-16.99 kg/m^2, severe = BMI 15-15.99 kg/m^2, extreme = BMI <15 kg/m^2), type (restricting = during last 3 mo no episodes of binge-eating or binge-eating/purging type = in last 3 mo have participated in recurrent episodes of binge-eating/purging)

Management
- standard work-up: vitals (weight and orthostatic BP and HR), bloodwork (CBC, electrolytes, creatinine, liver enzymes, B_{12}, TSH), ECG
- psychotherapy: individual, group, family; address food and body perception, coping mechanisms, health effects
- CBT: sets clear weight goals and expectations, makes use of recording sheets, targets maintaining factors such as negative body image
- family-based treatment is primarily used in the pediatric system, main focus is on weight restoration and return to physical health
- medications of little value; however, SSRIs may be helpful in treating concurrent mood and anxiety disorders
- outpatient and inpatient programs are available (nutritional rehabilitation)
- inpatient psychiatric hospitalization for treatment of eating disorders is rarely on an acute basis (unless there is a concurrent psychiatric reason for emergent admission (e.g. suicide risk)); such patients often require a specialized ED program
- criteria to admit to medical ward for hospitalization: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry (e.g. low K^+, low Mg^{2+}, Low PO_4^{3-}, high creatinine), or if actively suicidal
- agree on target body weight on admission and reassure this weight will not be surpassed
- monitor for complications of AN (see *Table 9, PS42*)
- monitor for refeeding syndrome
  - potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
  - complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium, and death
  - prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, and close monitoring of electrolytes and cardiac status

Prognosis
- adolescent onset has a much better prognosis than adult onset
- only about 50% make a full recovery
- with treatment, 70% resume a weight of at least 85% of expected levels and about 57% resume normal menstrual function
- eating abnormalities and associated psychiatric symptoms are common and persistent
- high rates of mortality (7%) secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion dying by suicide

Bulimia Nervosa

DSM-5 DIAGNOSTIC CRITERIA FOR BULIMIA NERVOSA
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A. recurrent episodes of binge-eating; an episode of binge-eating is characterized by both of the following:
  - eating, in a discrete period of time, an amount of food that is definitely larger than what most individuals would eat during a similar period of time and under similar circumstances
  - a sense of lack of control over eating during the episode

B. recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise

C. the binge-eating and inappropriate compensatory behaviours both occur, on average, at least once a week for 3 mo

D. self-evaluation is unduly influenced by body shape and weight

E. the disturbance does not occur exclusively during episodes of AN

- **specifiers**: partial remission, full remission, severity (mild = 1-3 inappropriate compensatory behaviours/wk, moderate = 4-7 inappropriate compensatory behaviours/wk, severe = 8-13 inappropriate compensatory behaviours/wk, extreme = 14+ inappropriate compensatory behaviours/wk)

Associated Features
- fatigue and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
- tooth decay, perioral irritation, mouth ulcers
- swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention, edema
- reddened knuckles, Russell's sign (knuckle callus from self-induced vomiting)
- trouble concentrating, fatigue, headache, abdominal pain/reflux
- weight fluctuation over time

Management
- medical admission for significant electrolyte abnormalities
- biological: treatment of starvation effects, SSRIs (fluoxetine has the most evidence) as adjunct
- psychological: develop trusting relationship with therapist to explore personal etiology and triggers, CBT, family therapy, recognition of health risks
- social: challenge destructive societal views of women, use of hospital environment to provide external patterning for normative eating behaviour

Prognosis
- relapsing/remitting disease
- good prognostic factors: onset before age 15, achieving a healthy weight within 2 yr of treatment
- poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance
- 60% good treatment outcome, 30% intermediate outcome, 10% poor outcome (mortality rate of approximately 2% per decade)

Binge-Eating Disorder

Definition
- recurrent episodes of binge-eating (as defined by criteria A of BN) that are associated with eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts when not physically hungry, eating alone because embarrassed by how much one is eating, and/or feeling disgusted with oneself/depressed/very guilty afterwards at least once/wk x 3 mo
- not associated with any compensatory behaviours
- dieting usually follows binge-eating (vs. BN where dysfunctional dieting typically precedes binge-eating)
- for more details about Binge-Eating Disorder, please consult the DSM-5

Epidemiology
- F:M=2:1
- begins in adolescence or young adulthood

Treatment
- CBT

Points for Differentiating Between Eating Disorders

AN of binge-eating/purging type (significantly low body weight) takes priority over a BN diagnosis (body weight not in criteria)

BN requires compensatory behaviours

Binge-eating disorder does not involve compensatory behaviours

Avoidant/restrictive food intake disorder does not involve disturbances in body image

Avoidant/Restrictive Food Intake Disorder

Definition
- eating/feeding disturbance (i.e. apparent lack of interest in eating or food) to the extent of persistent failure to meet appropriate nutritional and/or energy needs, resulting in significant weight loss/growth failure and nutritional deficiencies; patients experience disturbances in psychosocial functioning and may become dependent on enteral feeding/oral nutritional supplementation
  - does not occur during an episode of AN or BN and not better explained by lack of available food or culturally sanctioned practice
  - no evidence of distress in the way in which one's body weight or shape is experienced

Risk Factors
- temperament (e.g. anxiety disorders), environment (e.g. familial anxiety), genetic (e.g. history of GI conditions)
- begins in infancy and can persist into adulthood

Treatment
- psychoeducation
- behaviour modification
- psychotherapy

Important electrolytes in eating disorders: KPMg (potassium, phosphate, magnesium)

Table 9. Physiologic Complications of Eating Disorders

System	Starvation/Restriction	Binge-Purge
General	Low BP	Russell's sign (knuckle callus)
	Low HR	Parotid gland enlargement
	Significant orthostatic changes ± syncopal episodes	Perioral skin irritation and mouth ulcers
	Low body temperature	Periocular and palatal petechiae
	Vitamin deficiencies	Loss of dental enamel and caries
	Emaciation	Aspiration pneumonia
	Sleep disturbances	Metabolic alkalosis secondary to hypokalemia and loss of acid
	Fatigue/weakness	Fatigue
Endocrine	Primary or secondary amenorrhea, cold intolerance, decreased T3/T4	
Neurologic	Seizure (decreased Ca^{2+}, Mg^{2+}, PO_4^{3-})	
Cutaneous	Dry skin, lanugo hair, hair loss or thinning, brittle nails, yellow skin from high carotene	
GI	Constipation, GERD, delayed gastric emptying, abdominal pain	Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear
CVS	Arrhythmias, CHF	Arrhythmias, cardiomyopathy (from use of ipecac), sudden cardiac death (decreased K^+)
MSK	Osteoporosis secondary to hypogonadism	Muscle wasting
Renal	Pre-renal failure (hypovolemia), renal calculi	Renal failure (electrolyte disturbances)
Extremities	Pedal/periorbital edema (decreased albumin)	Pedal/periorbital edema (decreased albumin)
Lab Values	Starvation: decreased RBCs, decreased WBCs, decreased LH, decreased FSH, decreased estrogen, decreased testosterone, increased GH, increased cholesterol	Vomiting: decreased Na^+, decreased K^+, decreased Cl^-, decreased H^+; increased amylase; hypokalemia with metabolic alkalosis
	Dehydration: increased BUN	Laxatives: decreased Na^+, decreased K^+, decreased Cl^-, increased H^+; metabolic acidosis

Personality Disorders

- in the literature, personality and its disorders can be understood using a trait-based dimensional approach (i.e. 5 major traits such as extraversion, agreeableness, conscientiousness, neuroticism, and openness to experiences rated on a continuum of dysfunctional effects), rather than discrete categories; however, the discrete categories still remain in the current DSM and will be referenced here

General Information

- an enduring pattern of inner experiences and behaviours that deviate markedly from the expectations of the individual's culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- pattern is stable and well-established by adolescence or early adulthood (i.e. not a sudden onset)
- associated with many comorbidities such as depression, suicide, violence, brief psychotic episodes, substance use, and treatment resistance
- relationship building and establishing boundaries are important; focus should be placed on validating, finding things to be truly empathetic about, and speaking to the patient's strengths
- mainstay of treatment is psychotherapy (e.g. CBT, interpersonal psychotherapy, psychodynamic psychotherapy, DBT); add pharmacotherapy to treat associated psychiatric disorders (e.g. depression, anxiety, substance misuse)

A flag for personality disorders in clinical setting is the reaction that a patient is eliciting in you

Personality disorders with familial associations: schizotypal, antisocial, and borderline

Classification

- personality disorders are divided into three clusters (A, B, and C), with shared features among disorders within each

Table 10. Description and Diagnosis of Personality Disorders

Cluster A: "Mad" Personality Disorders
- Patients seem odd, eccentric, withdrawn
- Familial association with psychotic disorders
- Common defense mechanisms: intellectualization, projection, magical thinking

Paranoid Personality Disorder (1-4% of general population)	**Schizotypal Personality Disorder (4-5% of general population)**
Pervasive distrust and suspiciousness of others, interpret motives as malevolent Blame problems on others and seem angry and hostile Diagnosis requires 4+ of: **SUSPECT** 1. **S**uspicious that others are exploiting or deceiving them (without sufficient basis) 2. **U**nforgiving (bears grudges) 3. **S**pousal infidelity suspected without justification 4. **P**erceive attacks on character, counterattacks quickly 5. **E**nemies or friends? Preoccupied with acquaintance trustworthiness 6. **C**onfiding in others is feared 7. **T**hreats interpreted in benign remarks (**N**ote: **M**ust rule out psychotic disorder where no true delusions or hallucinations present)	Pervasive pattern of social and interpersonal deficits, cognitive/perceptual distortions, eccentric behaviours, and peculiar thought patterns Diagnosis requires 5+ of: **ME PECULIAR** 1. **M**agical thinking 2. **E**xperiences unusual perceptions (including body illusions) 3. **P**aranoid ideation 4. **E**ccentric behaviour or appearance 5. **C**onstricted or inappropriate affect 6. **U**nusual thinking/speech (e.g. vague, stereotyped) 7. **L**acks close friends 8. **I**deas of reference 9. **A**nxiety in social situations that does not diminish with familiarity (related to fears) (**N**ote: **R**ule out psychotic/pervasive developmental disorders - this is not part of the criteria; the more fixed and systematic a belief is, the more likely it is of delusional intensity)

Table 10. Description and Diagnosis of Personality Disorders

Schizoid Personality Disorder (3-5% of general population)
Neither desires nor enjoys close relationships including being a part of a family; prefers to be alone. Lifelong pattern of social withdrawal. Seen as eccentric and reclusive with restricted affect in a variety of contexts
Diagnosis requires 4+ of: **DISTANT**
1. **D**etached/flat affect, emotionally cold
2. **I**ndifferent to praise or criticism
3. **S**exual experiences of little interest
4. **T**asks done solitarily
5. **A**bsence of close friends (other than first-degree relatives)
6. **N**either desires nor enjoys close relationships (including family)
7. **T**akes pleasure in few (if any) activities

Cluster B: "Bad" Personality Disorders
- Patients seem dramatic, emotional, inconsistent, and impulsive
- Sensitive to perceived criticism, abandonment, or lack of attention; difficulty with interpersonal relationships due to self-serving, hostile, or erratic behaviour
- Familial association with mood disorders
- Common defense mechanisms: denial, acting out, regression (histrionic PD), splitting (borderline PD), projective identification, idealization/devaluation

Borderline Personality Disorder (1-2% of general population)
A pervasive pattern of instability of interpersonal relationships, self-image, and affects; marked impulsivity. Strong correlation with a history of childhood sexual abuse. Characterized by interpersonal, cognitive, behavioural, and affective deficits. Often exposed to an emotionally invalidating environment. The more dramatic behaviour tends to diminish as patients age. DBT is the principal treatment (see *Psychotherapy, PS48*)
10% suicide rate
Diagnosis requires 5+ of: **IMPULSIVE**
1. **I**mpulsive (minimum of 2 self-damaging ways, e.g. sex/drugs/spending)
2. **M**ood/affect instability
3. **P**aranoia or dissociation under stress
4. **U**nstable self-image
5. **L**abile intense relationships (extremes of idealization and devaluation)
6. **S**uicidal gestures/self-harm
7. **I**nappropriate anger
8. **V**oiding abandonment (real or imagined, frantic efforts to)
9. **E**mptiness (feelings of)
(Note: More frequently diagnosed in females but research suggests equal gender distribution)

Narcissistic Personality Disorder (around 6% of general population)
Sense of superiority, needs constant admiration, lacks empathy, but with fragile sense of self. Consider themselves "special" and will exploit others for personal gain. Beginning by early adulthood and present in a variety of contexts
Diagnosis requires 5+ of: **GRANDIOSE**
1. **G**randiose sense of self-importance (e.g. exaggerates achievements and talents)
2. **R**equires excessive admiration
3. **A**rrogant
4. **N**eeds to be special (and associate with other special or high-status people)
5. **D**reams of success, power, beauty, love (preoccupied with these fantasies)
6. **I**nterpersonally exploitative
7. **O**thers (lacks empathy, unable to recognize feelings/needs of others)
8. **S**ense of entitlement
9. **E**nvious (or believes others are envious)

Antisocial Personality Disorder (M: 2-4%, F: 0.5-1%)
Lack of remorse for actions, manipulative and deceitful, often violate the law. May appear charming on first impression. Pervasive pattern of disregard for others and violation of others' rights must be present before age 15; however, for the diagnosis of ASPD, patients must be at least 18. Must have evidence of conduct disorder before age 15; history of trauma/abuse common (see *Child Psychiatry, PS44*
Diagnosis requires 3+ of: **CORRUPT**
1. **C**annot conform to law and/or social norms (repeated illegal acts)
2. **O**bligations ignored (irresponsible)
3. **R**eckless disregard for safety of self or others
4. **R**emorseless
5. **U**nderhanded (deceitful; conning others for personal profit or pleasure)
6. **P**lanning insufficient (impulsive)
7. **T**emper (irritable and aggressive)

Histrionic Personality Disorder (2% of general population)
Attention-seeking behaviour and excessively emotional. Are dramatic, flamboyant, and extroverted. Cannot form meaningful relationships. Often sexually inappropriate. Diagnosed more in females but studies suggest equal prevalence
Diagnosis requires 5+ of: **ACTRESSS**
1. **A**ppearance used to attract attention
2. **C**entre of attention (else uncomfortable)
3. **T**heatrical
4. **R**elationships (believed to be more intimate than they are)
5. **E**asily influenced
6. **S**eductive behaviour
7. **S**hallow expression of emotions (which rapidly shift)
8. **S**peech (impressionistic and vague)

Cluster C: "Sad" Personality Disorders
- Patients seem anxious, fearful
- Familial association with anxiety disorder
- Common defense mechanisms: isolation, avoidance, hypochondriasis

Avoidant Personality Disorder (2.4% of general population)
Timid and socially awkward with a pervasive sense of inadequacy, social inhibition, and hypersensitivity to criticism. Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited
Diagnosis requires 4+ of: **CRINGES**
1. **C**riticism or rejection preoccupies thoughts in social situations
2. **R**estraint in relationships due to fear of being shamed
3. **I**nhibited in new relationships due to fear of inadequacy
4. **N**eeds to be sure of being liked before engaging socially
5. **G**ets around occupational activities requiring interpersonal contact
6. **E**mbarrassment prevents new activity or taking risks
7. **S**elf-viewed as unappealing or inferior

Obsessive-Compulsive Personality Disorder (2.1-7.9%)
Preoccupation with orderliness, perfectionism, and mental and interpersonal control. Is inflexible, closed-off, and inefficient. Highly comorbid with mood/anxiety and eating disorders
Diagnosis requires 4+ of: **SCRIMPER**
1. **S**tubborn
2. **C**annot discard worthless objects
3. **R**ule/detail obsessed (to point of activity lost)
4. **I**nflexible in matters of morality, ethics, values
5. **M**iserly
6. **P**erfectionistic to the extent that it hampers task completion
7. **E**xcludes leisure due to devotion to work
8. **R**eluctant to delegate to others

Dependent Personality Disorder (0.5-0.6% of general population)
Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviours. Difficulty making everyday decisions. Useful to set regulated treatment schedule (regular, brief visits) and being firm about in between issues. Encourage patient to do more for themselves, engage in own problem-solving
Diagnosis requires 5+ of: **RELIANCE**
1. **R**eassurance and/or advice required for everyday decisions (excessive)
2. **E**xpressing disagreement difficult
3. **L**ife responsibilities assumed by others
4. **I**nitiating projects difficult (because lack of self-confidence)
5. **A**lone (feels helpless and uncomfortable when alone)
6. **N**urturance (goes to excessive lengths to obtain)
7. **C**ompanionship sought urgently
8. **E**xaggerated fears of being left to care for self

Table 11. Key Differences Among Schizoid, Schizotypal, and Schizophrenia

	Schizoid	Schizotypal	Schizophrenia
Thought Form	Organized	Organized, but vague and circumstantial	Disorganized, tangential, loosening of associations
Thought Content	No psychosis	No psychosis; may have ideas of reference, paranoid ideation, odd beliefs, and magical thinking	Psychosis
Relationships	Solitary, NO desire for social relationships	Lacks close relationships, INTERESTED in relationships but has difficulty forming them	Socially marginalized, but not by choice

OCPD vs. OCD

	OCPD	OCD
Ego-Syntonic or Ego-Dystonic	Ego-syntonic	Ego-dystonic
Thought Content	Obsessional thinking, no compulsions, strict routine and rigidity in day-to-day matters, more perfectionistic and rigid	Obsessions and compulsions, rituals, anxiety provoking unwanted intrusive thoughts

Child Psychiatry

Developmental Concepts

- temperament: a child's innate psycho-physiological and behavioural characteristics (i.e. emotionality, activity, and sociability); spectrum from "difficult" to "slow-to-warm-up" to "easy temperament"
- parental fit: the congruence between parenting style (authoritative, permissive) and child's temperament
- attachment: special relationship between child and primary caretaker(s); develops during first year, the caretaker's attachment style is the best predictor of their child's attachment style, see *Table 12*
- separation anxiety (normal between 10-18 mo): where separation from attachment figure results in distress

Consider speaking to children alone. Always consider child abuse in your DDx. See Pediatrics, P18

Table 12. Attachment Models

Parent/Caregiver	Attachment Type	Features in Child (during Strange Situation experiment)
Loving, consistently available, sensitive, and receptive	Secure	Freely explores and engages with strangers well (as long as mother in close proximity), upset with caregiver's departure, happy with return
Rejecting, unavailable psychologically, insensitive responses	Insecure (avoidant)	Ignores caregiver, shows little emotion with arrival or departure, little exploration
Inconsistent, insensitive responses, role reversal	Insecure (ambivalent/resistant)	Clingy but inconsolable, often displays anger or helplessness, little exploration
Frightening, dissociated, sexualized, or atypical **Often history of trauma or loss**	Disorganized	Simultaneous approach/avoidance and stress-related straining behaviour

Tips for the Child Interview

Use language the child will understand (e.g. don't ask about feelings of worthlessness, ask about whether they feel like they are a bad kid)

Use developmentally-appropriate questions (e.g. don't ask about lack of interest in activities, ask children whether they feel bored)

Mood Disorders in Children and Adolescents

MAJOR DEPRESSIVE DISORDER

Epidemiology

- lifetime prevalence for pre-pubertal 1-2% (F:M=1:1); adolescents 4-18% (F:M=2:1)

Clinical Features

- only difference in diagnostic criteria for children and adolescents is that irritable mood may replace depressed mood
- physical features: insomnia (children), hypersomnia (adolescents), somatic complaints, substance misuse, decreased hygiene
- psychological features: irritability, boredom, anhedonia, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation, listlessness
- common comorbid diagnoses: anxiety, ADHD, ODD, conduct disorder, eating disorders, and substance misuse

Treatment

- majority never seek treatment
- supportive therapy including psychoeducation, active listening, and lifestyle advice helpful in mild depressive episode
- CBT or IPT, internet-based therapy if in-person options unavailable
- 1st line SSRI: fluoxetine
- 2nd line SSRIs: escitalopram, sertraline, citalopram
- close follow-up for adolescents starting SSRIs to monitor for increased suicidal ideation or behaviour
- in severe depression, combined pharmacotherapy and psychotherapy have best evidence of efficacy
- ECT or rTMS: limited evidence in this population, only for use in adolescents ≥12 y/o with severe illness, psychotic features, catatonic features, persistent suicidality
- light therapy, self-help books, and applications can be used as adjuncts

Prognosis
- prolonged episodes, up to 1-2 yr = poor prognosis
- prognosis variable; adolescents with depression more likely to have depression in adulthood than adolescents without
- approximately 2% of adolescents with depression will develop bipolar disorder within 4 yr
- complications: negative impact on family and peer relationships, school failure, significantly increased risk of suicide attempt or completion (however, suicide risk low for pre-pubertal children), substance use disorder

DISRUPTIVE MOOD DYSREGULATION DISORDER

Clinical Features
- severe, developmentally inappropriate, recurrent verbal or behavioural temper outbursts at least 3x/wk with persistently irritable mood in between
- symptom onset before age 10, occurring for ≥12 mo, in ≥2 settings, with no more than 3 consecutive mo free from symptoms
- diagnosis should be made between ages 6-18
- criteria not met for intermittent explosive disorder nor bipolar disorder (no mania/hypomania)
- supersedes diagnosis of ODD if criteria for both are met
- common comorbidities: ADHD, anxiety disorders, depressive disorders

BIPOLAR DISORDER

Clinical Features
- mixed presentation and psychotic symptoms (hallucinations and delusions) more common in adolescent population than adult population
  - often misdiagnosed in the adolescent population
- unipolar depression may be an early sign of adult bipolar disorder
- associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family, and pharmacologically-induced mania

Treatment
- lack of research in adolescent population, treatment guidelines based off of adult recommendations
- pharmacotherapy: mood stabilizers (lithium, anticonvulsants) and/or antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole)
- psychotherapy: CBT, family-focused therapy (a therapeutic modality designed for bipolar disorder that combines psychoeducation, communication skills training, and problem-solving skills training)

Anxiety Disorders in Children and Adolescents

- prevalence 10% in childhood/adolescence; F:M=2:1
- often not recognized

HEEADSSS Interview
Home environment
Education/Employment
Eating
Activities
Drugs
Sex
Safety
Suicide/depression

Clinical Features
- becomes problematic when it interferes with typical academic/social functioning
- children and adolescents may not vocalize their anxiety and instead may exhibit behavioural manifestations
- associated with school problems, unrealistic worries, physical/somatic symptoms (abdominal pain, headaches), social and relationship problems, social withdrawal and isolation, sleep difficulties, tearful episodes or temper tantrums, lack of confidence, irritability and mood symptoms, alcohol and drug use in adolescents
- tension may present as a physical sign, such as fidgeting

Differential Diagnosis
- depressive disorders, ODD, truancy
- persistence and impairment to daily functioning differentiates anxiety disorder from normal anxiety
- for school avoidance, differentiate social anxiety (fear of performance and humiliation) from generalized anxiety
- consider anxiety about separation, and rule out bullying and school refusal due to learning disorder

Course and Prognosis
- better prognosis with later age of onset, fewer comorbidities, early initiation of treatment, ability to maintain school attendance and peer relationships, and absence of social anxiety disorder
- with treatment, up to 80% of children will not meet criteria for their anxiety disorder at 3 yr follow-up, but up to 30% will meet criteria for another psychiatric disorder

Treatment
- similar principles for most childhood anxiety disorders due to overlapping symptomatology and frequent comorbidity
- psychoeducation of child and family
- psychotherapy: CBT has been shown to be effective in children and adolescents with anxiety
- pharmacotherapy: SSRIs can be helpful

SEPARATION ANXIETY DISORDER
- excessive and developmentally inappropriate anxiety on real, threatened, or imagined separation from attachment figures or home, with physical or emotional distress for at least 4 wk
- persistent worry about losing attachment figures or experiencing an untoward event to self; reluctance to go places, be alone, or sleep alone; nightmares involving separation; physical symptoms when separated
- often associated with school refusal, comorbid major depression

SOCIAL ANXIETY DISORDER (SOCIAL PHOBIA)
- anxiety, fear, and/or avoidance provoked by situations where child feels under the scrutiny of others
- must distinguish between shy child, child with issues functioning socially (e.g. autism), and child with social anxiety
  - diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning, or if markedly distressed. Must occur in settings with peers, not just adults
- features: crying, tantrums, freezing, clinging behaviour, mutism, excessively timid, stays on periphery, refuses to be involved in group play
- significant implication for future quality of life if untreated; lower levels of satisfaction in leisure activities, higher rates of school dropout, poor workplace performance, increased rates of remaining single

SELECTIVE MUTISM
- consistent failure to speak in specific social situations where speaking is expected, despite speaking in other situations for ≥1 mo
- the disturbance interferes with educational or occupational achievement or with social communication
- not due to lack of knowledge of language or communication disorder

GENERALIZED ANXIETY DISORDER
- diagnostic criteria same as adults (note: only 1 item is required in children for Criteria C)
- children worry about many things (e.g. school, future, family, past)
- often redo tasks, show dissatisfaction with their work, and tend to be perfectionistic
- often fearful in multiple settings and expect more negative outcomes when faced with academic or social challenges, and require reassurance and support to take on new tasks

SPECIFIC PHOBIA
- common phobias in childhood: fear of heights, small animals, physicians, dentists, darkness, loud noises, thunder, lightning

OCD
- diagnostic criteria same as adults
- note: young children may not be able to articulate the aims of their compulsions

Attachment type can be assessed in infants 10-18 mo of age using the Strange Situation test, in which the child is stressed by the caregiver being removed from the situation and the stranger staying. Attachment style is measured by the child's behaviour during the reunion with the caregiver

Attachment problems may present as a child who is difficult to soothe, has difficulty sleeping, problems feeding, tantrums, or behavioural problems

The shy child is quiet and reluctant to participate but slowly 'warms up'

Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: a Systematic Review and Meta-Analysis
JAMA Psychiatry 2017;74(10):1011-1020
Purpose: Examine the relative efficacy and safety of SSRIs, SNRIs, and placebo for the treatment of depressive disorders (DDs), anxiety disorders (ADs), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) in children and adolescents.
Methods: Meta-analysis of RCTs regarding use of SSRIs or SNRIs in youths with DD, AD, OCD, or PTSD. Effect sizes, calculated as standardized mean differences (Hedges g) and risk ratios (RRs) for adverse events, were assessed in a random-effects model.
Results: Thirty-six trials were eligible and analysis showed that SSRIs and SNRIs were more beneficial compared with placebo (g = 0.32; 95% CI, 0.25-0.40; P < .001). ADs (g = 0.56; 95% CI, 0.40-0.72; P < .001) had larger between-group effect sizes than DDs (g = 0.20; 95% CI, 0.13-0.27; P < .001). Patients with DDs exhibited significantly larger placebo responses (g = 1.57; 95% CI, 1.36-1.78; P < .001) compared with those with ADs (g = 1.03; 95% CI, 0.84-1.21; P < .001). The SSRIs produced a relatively large effect size for ADs (g = 0.71; 95% CI, 0.45-0.97; P < .001). Patients receiving an antidepressant vs. a placebo reported significantly more treatment-emergent adverse events (RR, 1.07; 95% CI, 1.01-1.12; P = .01 or RR, 1.49; 95% CI, 1.22-1.82; P < .001, depending on the reporting method), severe adverse events (RR, 1.76; 95% CI, 1.34-2.32; P < .001), and study discontinuation due to adverse events (RR, 1.79; 95% CI, 1.38-2.32; P < .001).
Conclusion: Compared with placebo, SSRIs and SNRIs are more beneficial than placebo in children and adolescents; however, the benefit is small and disorder specific, yielding a larger drug-placebo difference for AD than for other conditions. Response to placebo is large, especially in DD. Severe adverse events are significantly more common with SSRIs and SNRIs than placebo.

Neurodevelopmental Disorders

- Attention Deficit Hyperactivity Disorder (see Pediatrics, *Attention Deficit Hyperactivity Disorder*, P31)
- Autism Spectrum Disorder (see Pediatrics, *Autism Spectrum Disorder*, P30)

Disruptive, Impulse Control, and Conduct Disorder

Oppositional Defiant Disorder

- prevalence: 2-16%, M=F after puberty

Diagnosis

- pattern of negativistic/hostile and defiant behaviour for ≥6 mo, with ≥1 non-sibling, with ≥4 symptoms manifested in 3 areas of:
  - angry/irritable mood: easily loses temper, touchy or easily annoyed, often angry and resentful
  - argumentative/defiant: argues with adults/authority figure, defies requests/rules, deliberately annoys, blames others for their own mistakes or misbehaviour
  - vindictiveness: spiteful or vindictive twice in past 6 mo
  - note: difference between normal behaviour and ODD is frequency of symptoms (most days if age <5 yr, weekly if age ≥5 yr) exceeds what is normative for one's age, gender, culture
- behaviour causes significant distress or impairment in social, academic, or occupational functioning
- behaviours do not occur exclusively during the course of a psychotic, substance use, or mood disorder
- severity (mild/moderate/severe) according to number of settings in which symptoms are present
- diagnosis of disruptive mood dysregulation disorder supersedes ODD if criteria for both are met

Clinical Features

- first symptoms usually appear during preschool and rarely later than early adolescence
- associated with poor school performance, few friends, strained parent/child relationships, risk of developing mood disorders later on, often precedes CD

Treatment

- parent: parent management training, psychoeducation for parents and family
- behavioural therapy: to teach, practice, and reinforce prosocial behaviour
- social: school/day-care interventions
- pharmacotherapy for comorbid disorders

Conduct Disorder

- prevalence: 1.5-3.4% (M:F=4:1)

Etiology

- parental/familial factors: parental psychopathology (e.g. ASPD, substance use disorder), child-rearing practices (e.g. child abuse, discipline), low socioeconomic status (SES), family violence
- child factors: difficult temperament, ODD, learning problems, ADHD, neurobiology

Diagnosis

- pattern of behaviour that violates rights of others and age appropriate social norms with ≥3 criteria noted in past 12 mo and ≥1 in past 6 mo:
  - aggression to people and animals: bullying, initiating physical fights, use of weapons, forced sex, cruel to people and/or animals, stealing while confronting a person (i.e. armed robbery)
  - destruction of property: arson, deliberately destroying others' property
  - deceitfulness or theft: breaking and entering, conning others, stealing nontrivial items without confrontation
  - violation of rules: out all night before age 13, often truant from school before age 13, runaway ≥2 times at least overnight or for long periods of time
  - disturbance causes clinically significant impairment in social, academic, or occupational functioning
  - if ≥18 yr, criteria not met for ASPD
- diagnostic types
  - childhood-onset (≥1 criterion prior to age 10)
  - adolescent-onset (no criteria until age 10)
  - unspecified onset (insufficient information)
  - mild, moderate, severe
- differential: ADHD, depression, head injury, substance misuse

A Systematic Review and Analysis of Long-Term Outcomes in Attention Deficit Hyperactivity Disorder: Effects of Treatment and Non-Treatment
BMC Med 2012;10:99

Purpose: To determine the long-term outcomes of ADHD and whether there is an effect on long-term outcomes with treatment.

Methods: Systematic review of studies, including patients with diagnosed or symptomatic presentation of ADHD, assigned to pharmacological, non-pharmacological, multi-modal treatments, or a no-treatment control. Outcome measures included use/addictive behaviour, academic outcomes, antisocial behaviour, social function, occupation, self-esteem, driving outcomes, services use, and obesity.

Results: Untreated participants with ADHD had poorer outcomes vs. non-ADHD participants in 74% (n=244) of studies, while 26% (n=89) showed similar outcomes. 72% (n=37) of studies showed a benefit from ADHD treatment vs. untreated ADHD and 28% (n=15) showed no benefit. Treatment of ADHD was found to be beneficial in studies looking at driving (100%), obesity (100%), self-esteem (90%), social function (83%), academic outcomes (71%), drug use/addictive behaviour (67%), antisocial behaviour (50%), and occupation (33%).

Conclusion: Overall, people with ADHD have poorer long-term outcomes than controls (those without ADHD). For those with ADHD, treatment improves long-term outcomes.

Children with ODD like "RATs and BEARS"

Rule breaker
Annoying
Temper

Blames others
Easily annoyed
Argues with adults
Resentful
Spiteful/vindictive

Conduct Disorder Diagnosis

TRAP
Theft: breaking and entering, deceiving, non-confrontational stealing
Rule breaking: running away, skipping school, out late
Aggression: people, animals, weapons, forced sex
Property destruction

Treatment
- early intervention necessary and more effective; long-term follow-up required
- psychosocial: parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training
- pharmacotherapy for comorbid disorders

Prognosis
- poor prognostic indicators include: early-age onset, high frequency, variety of behaviours, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance misuse
- 50% of children with CD develop ASPD as adults

Intermittent Explosive Disorder

Diagnosis
- recurrent behavioural outbursts representing a failure to control aggressive impulses in children ages ≥6, manifested as either:
  - verbal or physical aggression that does not damage others or property, occurring ≥2 times per wk for 3 mo
  - 3 outbursts involving physical damage to another person, animal, or piece of property in the last 12 mo
- outbursts are out of proportion to triggers and are not premeditated/for primary gain
- outbursts cause clinically significant distress or impairment in occupation or interpersonal functioning, or financial/legal consequences
- diagnosis can be made in addition to ADHD, CD, ODD, or ASD diagnosis when recurrent outbursts are in excess of those usually seen in these disorders and warrant independent attention

See Pediatrics
- *Child Abuse,* P18, *Chronic Abdominal Pain,* P48, *Developmental Delay,* P26, *Intellectual Disability,* P27, *Learning Disabilities,* P29, *Sleep Disturbances,* P15

See Neurology
- *Tic Disorders, N35, Tourette's Syndrome, N35*

Psychotherapy

- treatment in which a person with mental or physical difficulties aims to achieve symptomatic relief through interactions with another person
- psychotherapy is delivered by a trained counsellor, social worker, nurse, psychologist, general practitioner, or psychiatrist
- various types of therapy exist based on diverse theories of human psychology and mental illness etiology

Common Factors of Psychotherapy
- good evidence that effective psychotherapy creates observable changes in brain circuitry and connectivity, but these changes are different from those observed with successful pharmacologic and other treatment modalities
- studies suggest that up to 60-90% of therapy outcome is due to common factors with only 10-40% due to specific factors
- common factors that predict positive outcomes are warmth (unconditional positive regard), accurate empathy, genuineness, goodness of fit, relationship with provider

Providing Anti-Oppressive Healthcare for Oppositional Defiant, Conduct, and Intermittent Explosive Disorders
Anti-oppressive healthcare recognizes health inequities and the impacts of historical and current trauma, including social and power imbalances, in communities. It is essential to recognize and address the effects of stigmatization, discrimination, and other forms of oppression on people who have historically experienced and continue to experience health inequities. Providing care that is culturally safe, antiracist, gender-affirming, and trauma-informed is crucial. Practitioners should reflect on their intersectional identities, privileges, oppressions, assumptions, and biases, and recognize how they influence clinical practice. Practitioners should also assess and address biases in clinical reasoning to prevent under-, over- and misdiagnosis.

Table 13. Summary of Psychotherapeutic Modalities

Type	Indications	Approach, Technique, and Theory	Ideal Candidates	Duration
Supportive Therapy	Adjustment disorders, somatic symptoms and related disorders, severe psychotic or personality disorders Adjunct to pharmacologic management in most disorders	Uses empathy, validation, and reflection to facilitate adaptation and coping Help patients feel safe, secure, and encouraged	Individuals in crisis or with severe symptoms in acute or chronic settings	Variable (single session to years, though often short-intermittent)
Interpersonal Therapy	Mood disorders	Focuses on how interpersonal relationships impact symptoms 4 key problem areas addressed: 1. grief and loss, 2. role transitions, 3. conflict, 4. interpersonal deficits Break the interpersonal cycle: depression, self-esteem, social withdrawal	Individuals with depression or bipolar disorder with some insight and difficult social functioning Absence of severe psychotic process, personality disorder, or comorbid substance use disorder	Weekly sessions, 12-20 sessions
Cognitive Behavioural Therapy	Most mental health disorders including: mood, anxiety, OCD, personality, eating, substance use, psychotic disorders	Combines theory and method from cognitive and behavioural therapies to teach the patient to change connections between thinking patterns, habitual behaviours, and mood/anxiety problems Cognitive component includes using thought records to help monitor thoughts and identify inaccurate automatic thoughts Behavioural component includes techniques such as systematic desensitization (mastering anxiety-provoking situations by approaching them gradually and in a relaxed state that limits anxiety), flooding (confronting feared stimulus for prolonged periods until it is no longer frightening), positive reinforcement (strengthening behaviour and causing it to occur more frequently by rewarding it), negative reinforcement (causing behaviour to occur more frequently by removing a noxious stimulus when desired behaviour occurs), extinction (causing a behaviour to diminish by not rewarding it), and punishment/aversion therapy (causing a behaviour to diminish by applying a noxious stimulus)	Individuals with motivation to change and who are able to participate in homework	Typically weekly or twice weekly sessions, 12-20 sessions Maintenance therapy can be carried out over years
Dialectical Behavioural Therapy	Borderline personality disorder	Therapy that combines CBT techniques with Buddhist Zen mindfulness practices and dialectical philosophy Focuses on 4 types of skills: mindfulness, emotional regulation, interpersonal effectiveness, and distress tolerance Involves 4 components: individual therapy, group skills training, phone consultations, and a consultation team	Individuals with borderline personality disorder or borderline personality trait and severe problems of emotional dysregulation, impulsivity, or self-harm	Typically 1 yr Weekly individual and group therapy
Motivational Interviewing and Motivational Enhancement Therapy	Substance use disorders Techniques can be applied to facilitate behavioural change in most psychological problems	Spirit of MI (CAPE): Compassion, Acceptance, Partnership, Evocation Principles of MI (RULE): Resist "righting reflex", Understand client and their reasons for change, Listen, Empower by conveying hope and supporting autonomy Techniques of MI (OARS): Open-ended questions, Affirmations to validate client, Reflections (the skill of accurate empathy), Summaries to help client organize self	Individuals with problematic substance use, maladaptive behaviour patterns (therapy disengagement, medication noncompliance, poor health habits)	Brief interventions (efficacy with as little as 15 min, single session), better result with more sessions Addiction is a chronic condition, often need boosters over time MET = 4 sessions
Group Psychotherapy	Most mental health disorders including mood, anxiety, OCD, personality, eating, substance use, and psychotic disorders can benefit from group therapy as part of treatment	Aims to promote self-understanding, acceptance, social skills	Adolescents, individuals not currently in crisis, absence of severe psychotic symptoms	Variable Often time-limited (e.g. weekly sessions for 12 wk)
Family Therapy	Most mental health disorders including mood, anxiety, OCD, personality, eating, substance use, and psychotic disorders can benefit from group therapy as part of treatment	Family system considered more influential than individual, especially for children Focus on here and now, re-establishing parental authority, strengthening normal boundaries, and rearranging alliances	Children and adolescents with families willing to engage in treatment	Often short-term (e.g. 12 sessions)
Mindfulness-based Cognitive Therapy/ Mindfulness-based Stress Reduction	Emerging evidence for treating adjustment disorder, MDD (relapse prevention), anxiety, pain disorders, insomnia, substance use disorder (relapse prevention)	Derived from Buddhist meditative and philosophical practices; aims to help people attend to thoughts, behaviours, and emotions in the moment and non-judgmentally using guided breathing exercises	Individuals who are motivated and willing to engage in therapy	Generally weekly sessions for 8 wk
Psychoanalytic/ Psychodynamic Therapy	Anxiety, obsessional thinking, conversion disorder, depression	Theory: exploration of meaning of early experiences and how they affect emotions and patterns of behaviour Recollection (remembering), repetition (reliving with the therapist), working through (gaining insight) Techniques: free association, dream interpretation, transference analysis	Psychologically minded, highly motivated, wish to understand selves and not just relieve symptoms Able to withstand difficult emotions without fleeing or self-destructive acts High level of function	Time intensive: Psychoanalysis: 4-5 times/wk for 3-7 yr Psychodynamically oriented therapy: 2-3 times/wk for fewer yr

Pharmacotherapy

Antipsychotics

- "antipsychotics" used to be called "neuroleptics"
- overall mechanism of action: functionally antagonize, to varying degrees, D2 activity in target brain pathways
- primarily indicated for psychotic symptoms in: schizophrenia and related disorders, manic episodes, depressive episodes, substance use, medical conditions (e.g. neoplasm)
- other uses: treatment-resistant MDD, severe GAD, complex PTSD, severe OCD, borderline PD, behavioural symptoms of dementia, delirium, Tourette syndrome, substance use disorder in dual diagnosis, Huntington's disease, ASD, and impulse control disorders
  - adjunctive management of agitation, aggression, severe anxiety, and severe sleep difficulties when sedative-hypnotics are contraindicated
- onset: acute, rapid calming effect and decrease in agitation; antipsychotic effect with improvement in thought disorder, delusions, and hallucinations may take 1-4 wk
- rational use
  - current guidance states there is no reason to combine two or more antipsychotics, although this is quite common in clinical practice and evidence is changing rapidly
  - all antipsychotics are equally effective, except for clozapine (considered to be most effective in treatment-resistant schizophrenia)
  - atypical antipsychotics (i.e. second generation) are as effective as typical (i.e. first generation) antipsychotics and have different adverse effect profiles; main difference is lower risk of EPS and TD but more metabolic side effects (see sidebar)
  - choose a drug to which the patient has responded to in the past or that was used successfully in a family member
- route: PO, short-acting or long-acting depot IM injections, and sublingual; more recently there is inhaled loxapine mainly used in the setting of acute agitation
- if no robust response in 4-6 wk, switch drugs
- duration: minimum 6 mo and usually for life in most patients with primary psychotic disorders; variable for other indications

Long-Acting Preparations

- antipsychotics formulated in oil for IM injection
- received on an outpatient basis
- indications: initially meant for individuals with schizophrenia or other chronic psychosis who relapse because of non-adherence, but current initial evidence suggests they are better than oral preparations overall
- should have been exposed to oral or short term injectable form prior to first injection
- dosing: there are generally equivalence tables for oral dosing, or pre-set starting schedules
- side effects: similar to side effect profile to oral preparation of the same drug; may be pain at the site of injection

Canadian Guidelines for the Treatment of Acute Psychosis in the Emergency Setting

- haloperidol 5 mg IM ± lorazepam 2 mg IM
- loxapine PO or IM 25 mg ± lorazepam 2 mg IM
- olanzapine 2.5-10 mg (PO, IM, oral quick dissolve – its time to peak is the same as regular PO, 4-6 h)
- risperidone 2 mg (M-tab, liquid)

Dopamine Pathways Affected by Antipsychotics

Pathway	Effects	Associated Pathology
Mesolimbic	Emotion origination, reward	HIGH dopamine causes positive symptoms of schizophrenia (delusions, hallucinations)
Mesocortical	Cognition, executive function	LOW dopamine causes negative symptoms of schizophrenia
Nigrostriatal	Movement	LOW dopamine causes EPS
Tubero-infundibular	Prolactin hormone release	LOW dopamine causes hyper-prolactinemia

Typical (First Generation) vs. Atypical (Second Generation) Antipsychotics

	Typical	Atypical
Mechanism	Block postsynaptic dopamine receptors (D2)	Block postsynaptic dopamine receptors (D2) Block serotonin receptors (5-HT2) on presynaptic dopaminergic terminals, triggering DA release, and reversing DA blockade in some pathways. Some are partial D2 agonists
Pros	Inexpensive Plenty of injectable forms available	EPS less prevalent Low-risk of tardive syndromes Mood stabilizing effects
Cons	EPS more prevalent, including tardive syndromes in long-term Not mood stabilizing	Expensive Few injectable forms available Metabolic side effects (weight gain, hyperglycemia, lipid abnormalities, metabolic syndrome) Exacerbation (or new onset) of obsessive behaviour

Anticholinergic Effects		
Red	as a	beet
Hot	as a	hare
Dry	as a	bone
Blind	as a	bat
Mad	as a	hatter

Table 14. Common Antipsychotic Agents

	Starting Dose	Maintenance	Maximum	Relative Potency (mg)
Typicals (in order of potency from high to low)				
Haloperidol (Haldol®)	2-5 mg IM q4-8 h 0.5-5 mg PO B/TID 0.2 mg/kg/d PO	Based on clinical effect	20 mg/d PO	2
Zuclopenthixol HCl (Clopixol®)	20-30 mg/d PO	20-40 mg/d PO	100 mg/d PO	4
Zuclopenthixol acetate (Acuphase®)	50-150 mg IM q48-72 h		400 mg IM (q2 wk)	
Zuclopenthixol decanoate (Cloxipol Depot®)	100 mg IM q1-4 wk	150-300 mg IM q2 wk	600 mg IM/wk	
Perphenazine (Trilafon®)	8-16 mg PO B/TID	4-8 mg PO T/QID	64 mg/d PO	10
Loxapine HCl (Loxitane®)	10 mg PO TID 12.5-50 mg IM q4-6 h	60-100 mg/d PO	250 mg/d PO	10
Chlorpromazine (Largactil®)	10-25 mg PO B/T/QID	400 mg/d PO	1000 mg/d PO	100
Atypicals (in order of potency from high to low)				
Risperidone (Risperdal®, Risperdal Consta® for IM long acting preparation, Risperdal® M-Tab for melting form – placed on tongue)	1-2 mg once daily/BID	4-8 mg/d PO 25 mg IM q2 wk	8 mg/d PO	2
Paliperidone (Invega®, Invega Sustenna® (one v) or Trinza® (three months) for IM long acting preparations)	3 mg/d PO	3-12 mg/d PO	12 mg/d PO	4
Olanzapine (Zyprexa®, Zyprexa Zydis® for melting form – placed on tongue)	5 mg/d PO	10-20 mg/d PO	30 mg/d PO	5
Asenapine (Saphris®)	5 mg SL BID	5-10 mg SL BID	10 mg SL BID	5
Ziprasidone (Zeldox®)	20 mg PO BID	40-80 mg PO BID	160 mg/d PO	6
Aripiprazole (Abilify®)	10-15 mg/d PO	10-15 mg/d PO	30 mg/d PO	7.5
Quetiapine (Seroquel®, Seroquel XR® for extended release®)	25 mg PO BID	400-800 mg/d PO	800 mg/d PO	75
Lurasidone (Latuda®) Has to be taken with at least 350 kcal meal	20 mg PO	40-80 mg/d PO	160 mg/d PO	
Clozapine (Clozaril®)	25 mg PO BID	300-600 mg/d PO	900 mg/d PO	100

See Landmark Psychiatry Trials table for more information on CATIE, which details a comparison between first and second-generation antipsychotics in the treatment of schizophrenia.

Metabolic and Cardiovascular Adverse Effects Associated with Antipsychotic Drugs
Nat Rev Endocrinol 2012;8:114-126
All atypical antipsychotics can cause cardiovascular and metabolic side effects, such as obesity, dyslipidemia, hyperglycemia, and weight gain. Olanzapine and clozapine are most likely to cause these adverse effects. The mechanism that underlies the metabolic and cardiovascular effects is not fully understood. However, the histamine, dopamine, serotonin, and muscarinic receptors are implicated.

QTc prolongation is an important adverse effect of all antipsychotics; although not required, consider getting ECG prior to and after initiating new medication and to monitor QTc
Typicals: chlorpromazine and haloperidol warrant systematic baseline and follow-up ECG
Atypicals: ziprasidone has the highest risk among atypicals, clozapine also warrants systematic baseline and follow-up ECG

Features of Neuroleptic Malignant Syndrome

FARM
Fever
Autonomic changes (e.g. increased HR/BP, sweating)
Rigidity of muscles
Mental status changes (e.g. confusion)

FARM symptoms are also seen in serotonin syndrome (SS)
SS can be distinguished from NMS by the following:

SS	NMS
Twitchy, shivering, restless	Severe global rigidity
Flushed, sweaty	Pallor
Vomiting, diarrhea, abdominal pain	No GI symptoms

Table 15. Commonly Used Atypical Antipsychotics

	Risperidone (Risperdal®)/ Paliperidone (Invega®)	Olanzapine (Zyprexa®, Zydis®)	Quetiapine (Seroquel®)	Clozapine (Clozaril®)	Aripiprazole (Abilify®)
Advantages	Lower incidence of EPS than typical antipsychotics at lower doses (<8 mg) Associated with less weight gain compared to clozapine and olanzapine	Better overall efficacy compared to haloperidol Well tolerated Low incidence of EPS and TD	Associated with slightly less weight gain compared to clozapine and olanzapine, but more than the other atypicals Mood stabilizing	Most effective for treatment-resistant schizophrenia Does not worsen tardive symptoms; may treat them Approximately 50% of patients benefit, especially paranoid patients and those with onset after 20 yr	Less weight gain and risk of metabolic syndrome compared to olanzapine and a lower incidence of EPS compared to haloperidol Mood stabilizing
Disadvantages Relative to Other SGAs	Highest risk of EPS/TD among SGAs – avoid if high-risk for EPS or existing movement disorder or elderly Elevated prolactin - sexual dysfunction, galactorrhea, gynecomastia, menstrual disturbance, infertility	Weight gain and metabolic effects – avoid in DM Sedating – avoid if high-risk for falls or fracture	Sedating/orthostatic hypotension – avoid if high-risk for falls or fracture QT prolongation in high doses – caution if cardiac risk	Weight gain and metabolic effects- avoid in DM Sedating/orthostatic hypotension - avoid if high-risk for falls or fracture Potentially severe constipation - avoid if risk of fecal impaction or bowel perforation Cardiomyopathy – caution if existing heart disease Reduces seizure threshold - caution if seizure disorder Agranulocytosis (1%) – avoid in existing leukopenia/ neutropenia, requires ongoing CBC monitoring	Insomnia, akathisia
Comments	Quick dissolve (M-tabs), and long-acting (Consta®/ Invega Trinza®) formulations available	Quick dissolve formulation (Zydis®) used commonly in ER setting for better compliance (but does not act faster) Acute IM form available		Weekly blood counts for 6 mo, then q2 wk Do not use with other drugs that may cause bone marrow suppression due to risk of agranulocytosis	

Note: Risk of weight gain: Clozapine > Olanzapine > Quetiapine > Risperidone

Table 16. Side Effects of Antipsychotics

System	Side Effects
Anticholinergic	Dry mouth, urinary retention, constipation, blurred vision, confusional states
α-adrenergic Blockade	Orthostatic hypotension, erectile dysfunction, failure to ejaculate
Dopaminergic Blockade	Extrapyramidal syndromes, galactorrhea, amenorrhea, erectile dysfunction, weight gain
Anti-Histamine	Sedation, weight gain
Hematologic	Agranulocytosis (clozapine)
Hypersensitivity Reactions	Liver dysfunction, blood dyscrasias, skin rashes, neuroleptic malignant syndrome, altered temperature regulation (hypothermia or hyperthermia)
Endocrine	Metabolic syndrome
Cardiac	QT prolongation

Neuroleptic Malignant Syndrome

- psychiatric emergency
  - hypothesis: due to strong DA blockade; increased incidence with high potency and depot antipsychotics
- risk factors
  - medication factors: sudden increase in dosage, starting a new drug
  - patient factors: medical illness, dehydration, exhaustion, poor nutrition, external heat load, male, young adults
- clinical features
  - tetrad: mental status changes (usually occur first), fever, rigidity, autonomic instability
  - develops over 24-72 h
  - labs: increased creatine phosphokinase, leukocytosis, myoglobinuria
- treatment: supportive - discontinue antipsychotic drug, hydration, cooling blankets, dantrolene (hydantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)
- mortality: 5%

Extrapyramidal Symptoms

- incidence related to increased dose and potency
- acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)

Table 17. Extrapyramidal Symptoms

	Dystonia	Akathisia	Parkinsonism	Dyskinesia
Acute or Tardive	Both (mainly acute)	Both	Acute	Tardive
High-Risk Groups	Acute: young Asian and Black males	Older females	Older females	Older patients
Presentation	Sustained contraction of muscle groups; abnormal posture; torsions, twisting, muscle spasms (i.e. oculogyric crisis, laryngospasm, torticollis)	Motor restlessness; crawling sensation in legs relieved by walking; very distressing, increased risk of suicide and poor adherence	Tremor; rigidity (cogwheeling); akinesia; postural instability (decreased/absent arm-swing, stooped posture, shuffling gait, difficulty pivoting)	Purposeless, involuntary, constant movements that involve facial and mouth musculature; less commonly – the limbs; rarely, the diaphragm ("hiccups")
Onset	Acute: within 5 d Tardive: >90 d	Acute: within 10 d Tardive: >90 d	Acute: within 30 d	Tardive: >90 d, more commonly yr
Treatment	Acute: benztropine or diphenhydramine, usually IM	Acute: lorazepam, propranolol, benztropine, or diphenhydramine; best approach: reduce dose or change antipsychotic to lower potency	Acute: benztropine; reduce dosage or change antipsychotic to low potency atypical antipsychotic	Tardive: no good treatment; may try clozapine; discontinue drug or reduce dosage Recently the FDA approved valbenazine and deutetrabenazine for the treatment of tardive dyskinesia

Anticholinergic Agents

- types
  - benztropine (Cogentin®) 2 mg PO, IM, or IV once daily (1-6 mg)
  - diphenhydramine (Benadryl®) 25-50 mg PO/IM QID
- do not routinely prescribe with antipsychotics
  - give anticholinergic agents only if at high-risk for acute EPS or if acute EPS develops
- do not give these for tardive syndromes because they worsen the condition

Antidepressants

- onset of effect
  - relief of neuro-vegetative/physical symptoms: 1-3 wk
  - relief of emotional/cognitive symptoms: 2-6 wk
- tapering of most antidepressants is usually required to avoid withdrawal reactions; speed of taper is based on the medication's half-life and the patient's individual sensitivity (i.e. fluoxetine does not require a taper due to its long half-life; paroxetine and venlafaxine require a slower taper than sertraline or citalopram)
- must be vigilant over the first 2 wk of therapy; neuro-vegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be at risk for suicidal behaviour during this time, particularly in children/adolescents)
- treatment of bipolar depression
- patients with bipolar disorder (bipolar depression) should not be treated with an antidepressant as the first-line therapy
  - patients with bipolar disorder should only be treated with an antidepressant if combined with a mood stabilizer or antipsychotic; monotherapy with antidepressants is not advisable as it may provoke the emergence of mania
  - maintenance of patients with bipolar disorder with antidepressants is not advisable except in specific cases

Table 18. Common Antidepressants

Class	Drug	Daily Starting Dose (mg)*	Therapeutic Dose (mg)	Comments
SSRI	fluoxetine (Prozac®) fluvoxamine (Luvox®) paroxetine (Paxil®) sertraline (Zoloft®) citalopram (Celexa®) escitalopram (Cipralex®)	20 50-100 10 50 20 10	20-80 150-300 20-60 50-200 20-40 10-20	seful for typical and atypical depression, seasonal depression, anxiety disorders, OCD, eating disorders All SSRIs have similar effectiveness but consider side effect profiles and half-lives Citalopram and escitalopram have the fewest drug interactions and are sleep-wake neutral Sertraline is the safest SSRI in pregnancy and breastfeeding Fluoxetine is the most activating SSRI (recommend taking in the AM) Fluoxetine does not require a taper due to long half-life and is the most used in children and adolescents as it has most evidence in that age group Fluvoxamine is sedating (should be taken in PM) and can be involved in many drug-drug interactions For OCD, aim for maximum doses, sometimes higher
SNRI	venlafaxine (Effexor®) desvenlafaxine (Pristiq®) duloxetine (Cymbalta®)	37.5-75 50 30	75-225 50-100 30-60	Useful for depression, anxiety disorders, neuropathic pain
NDRI	bupropion (Wellbutrin®)	100	300-450	Useful for depression, seasonal depression; not recommended for anxiety disorders treatment because of stimulating effects Causes less sexual dysfunction (may reverse this effects of SSRIs/SNRIs), weight gain, and sedation Increased risk of seizures at higher doses Contraindicated with history of seizure, stroke, brain tumour, brain injury, closed head injury Important to specify formulation, as available in IR, SR, XL (longest)
TCA (3° Amines)	amitriptyline (Elavil®) imipramine (Tofranil®) clomipramine (Anafranil®)	25-50 25-50 25-50	150-300 150-300 100-250	Useful for OCD (clomipramine is gold standard), melancholic depression, can also be used in other types of depression and anxiety disorders Requires ECG monitoring Check blood levels if using higher dosage Highly lethal in overdose
TCA (2° Amines)	nortriptyline (Aventyl®) desipramine (Norpramin®)	25-50 25-50	75-150 150-300	Preferred to tertiary amines because of lower propensity for anticholinergic adverse effects Requires ECG monitoring Check blood levels if using higher dosage Highly lethal in overdose
MAOI	phenelzine (Nardil®) tranylcypromine (Parnate®)	15 20	60-90 10-60	Useful for moderate/severe depression that does not respond to other antidepressants; atypical depression; anxiety disorders Requires strict adherence to MAOI diet, (low tyramine)
RIMA	moclobemide (Manerix®)	300	300-600	Useful for some anxiety disorders (e.g. social phobia) and depression MAOI diet is required
NaSSA	mirtazapine (Remeron®)	15	15-45	Useful in depression with prominent features of insomnia, agitation, or cachexia Sedative is useful when insomnia is an issue
SPARI	vilazodone (Viibryd®)	10	10-40	Useful in those with constipation as diarrhea is a common side effect
Serotonin Receptor Modulator	vortioxetine (Trintellix®)	5	5-20	May improve cognitive function

*for depression (start with ½ this dose for treatment of anxiety disorders)

MAOI = monoamine oxidase inhibitors; NaSSA = noradrenergic and specific serotonergic agent; NDRI = norepinephrine and dopamine reuptake inhibitors; RIMA = reversible inhibition of MAO-A; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; SPARI = serotonin partial agonist and reuptake inhibitor

Treatment Approach for Depression

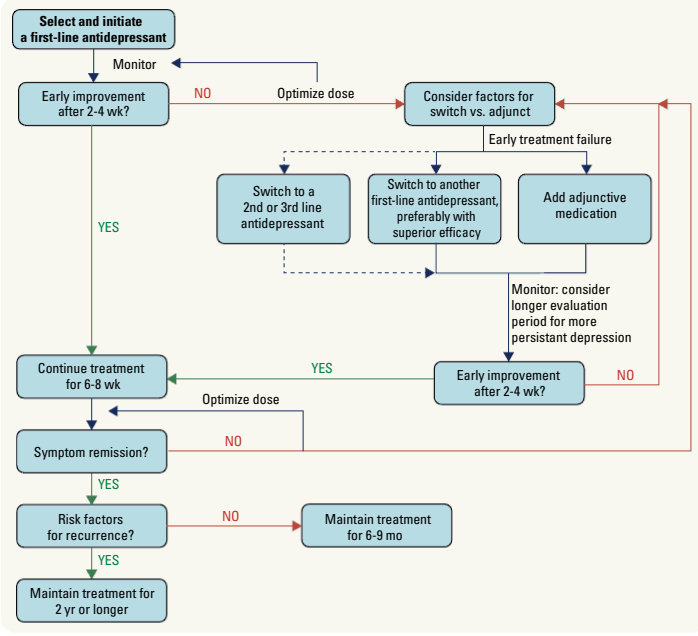

Figure 3. Depression treatment algorithm
Adapted from: Sidney H. Kennedy, Raymond W. Lam, Roger S. McIntyre, et al, The Canadian Journal of Psychiatry (61, 9), p. 21, copyright © 2020, Modified by Permission of SAGE Publications, Inc.

- **optimization**: increase dosage to maximum tolerated or highest therapeutic dosage
- **augmentation**: the addition of a medication that is not considered an antidepressant to an antidepressant regimen (i.e. thyroid hormone, lithium, atypical antipsychotics (aripiprazole, quetiapine, olanzapine, risperidone))
- **combination**: the addition of another antidepressant to an existing treatment regimen (i.e. the addition of bupropion or mirtazapine to an SSRI or SNRI)
- **switch**: change of the primary antidepressant (within or outside a class)
- note: it is important to fully treat depression symptoms (i.e. to remission) to decrease relapse rates

Serotonin Syndrome

- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as more than one SSRI, SSRI + SNRI, SSRI or SNRI + MAOI, SSRI + tryptophan, MAOI + meperidine, MAOI + tryptophan
- rare but potentially life-threatening adverse reaction to SSRIs and SNRIs
- symptoms include: nausea, diarrhea, palpitations, chills, diaphoresis, restlessness, confusion, and lethargy, but can progress to myoclonus, hyperthermia, rigor, and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS

Discontinuation Syndrome

- caused by the abrupt cessation of some antidepressants; most commonly with paroxetine, fluvoxamine, and venlafaxine (drugs with shortest half-lives)
- symptoms usually begin within 1-3 d and can include anxiety, insomnia, irritability, mood lability, N/V, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy, and myalgia ("flu-like symptoms")
- treatment: symptoms may last between 1-3 wk, but can be relieved within 24 h by restarting antidepressant at the same dosage the patient was taking initially and initiating a slower taper over several weeks
- consider avoiding drugs with a short half-life

Psychopharmacology of SSRIs

Post-Synaptic Serotonin Receptor Stimulated	Effect/Side Effect
5HT1A centrally	Relief of depression Anxiolytic effect
5HT2A in spinal cord	Sexual dysfunction: delayed ejaculation, anorgasmia, decreased interest/ libido
5HT2C/5HT2A in brain	Activation: anxiety, insomnia Worst with fluoxetine, paroxetine Warn patients anxiety may worsen in first 1-2 wk of treatment
5HT3A in gut	GI upset: nausea, vomiting, bloating Take with food

Symptoms of Antidepressant Discontinuation (mainly from serotonin reuptake inhibition activity)

FINISH
Flu-like symptoms
Insomnia
Nausea
Imbalance
Sensory disturbances
Hyperarousal (anxiety/agitation)

Table 19. Features of Commonly Used Antidepressant Classes

	SSRI	SNRI	TCA	MAOI	NDRI	RIMA	NaSSA	SPARI	Serotonin receptor modulator
Examples	fluoxetine, sertraline, citalopram	venlafaxine, duloxetine	amitriptyline, clomipramine	phenelzine	bupropion	moclobemide	mirtazapine	vilazodone	vortioxetine
Mode of Action	Block serotonin reuptake only	Block norepinephrine and serotonin reuptake	Block norepinephrine reuptake (clomipramine also blocks serotonin reuptake)	Irreversible inhibition of MAO A and B increases duration that NE, dopamine, and 5HT are in the synaptic cleft by preventing their degradation	Block norepinephrine and dopamine reuptake	Reversible inhibitor of monoamine oxidase A leads to increased duration of norepinephrine, dopamine, and 5HT in the synaptic cleft by preventing their degradation	Enhance central noradrenergic and serotonergic activity by inhibiting presynaptic α-2 adrenergic receptors	5HT1A partial agonism causes downregulation of presynaptic 5HT1A receptors to disinhibit serotonin release, and 5HT4 agonism treats constipation	5HT1A agonism downregulates presynaptic 5HT1A receptors to disinhibit serotonin release, and 5HT7 antagonism theoretically enhances cognitive function
Side Effects	CNS: restlessness, tremor, insomnia, headache, drowsiness, EPS GI: N/V, diarrhea, abdominal cramps, weight gain Sexual dysfunction: erectile dysfunction, anorgasmia CVS: increased HR, increased QTc, serotonin syndrome, SIADH, decreased platelet aggregation – increased risk of bleeding	Low dose side effects similar to SSRIs (serotonergic) Higher dose side effects: tremors, tachycardia, sweating, insomnia, orthostatic hypotension, increase in BP (noradrenergic) SIADH	Anticholinergic effects: (see *Table 16, PS52*) Noradrenergic effects: tremors, tachycardia, sweating α-1 adrenergic effects: orthostatic hypotension, falls QRS prolongation	Antihistamine effects (minimal): sedation, weight gain CVS: orthostatic hypotension, hypertensive crises with tyramine rich foods (e.g. wine, cheese), or combination with serotonergic or adrenergic medications, headache, flushes, reflex tachycardia, postural hypotension, insomnia Minimal anticholinergic effects	CNS: dizziness, headache, tremor, insomnia, agitation, anxiety, lower seizure threshold CVS: dysrhythmia, HTN GI: dry mouth, N/V, constipation, decreased appetite	CNS (usually minor): dizziness, headache, tremor, insomnia CVS: dysrhythmia, hypotension GI: dry mouth, N/V, diarrhea, abdominal pain, dyspepsia GU: delayed ejaculation Other: diaphoresis	CNS: sedation, dizziness Endocrine: increase in cholesterol, increase in triglycerides, weight gain GI: constipation, ALT elevation	CNS: sedation GI: nausea, diarrhea	GI: nausea
Risk in Overdose	Relatively safe in overdose	Tachycardia and N/V seen in acute overdose	Toxic in overdose 3 times therapeutic dose may be lethal Presentation: anticholinergic effects, CNS stimulation, then depression and seizures ECG: prolonged QRS and QTc (reflect severity) Treatment: activated charcoal, cathartics, supportive treatment, IV diazepam for seizure, physostigmine salicylate for coma Do not give ipecac, as can cause rapid neurologic deterioration and seizures	Toxic in overdose, but wider margin of safety than TCA	Tremors and seizures seen in overdose	Risk of fatal overdose when combined with SSRIs, SNRIs, or clomipramine	Relatively safe in overdose	Relatively safe in overdose	Relatively safe in overdose
Drug Interactions	MAOI, SNRI Some SSRIs (fluoxetine, fluvoxamine, paroxetine) strongly inhibit cytochrome P450 enzymes, therefore will affect levels of drugs metabolized by P450 system	MAOI, SSRI Low inhibition of cytochrome P450 compounds	MAOI, SSRI EtOH	Hypertensive crises with noradrenergic medications (i.e. TCA, decongestants, amphetamines) Serotonin syndrome with serotonergic drugs (i.e. SSRI, SNRI, tryptophan, dextromethorphan)	MAOI Drugs that reduce seizure threshold: antipsychotics, systemic steroids, quinolone antibiotics, antimalarial drugs	MAOI, paroxetine Opioids	MAOI, RIMA	MAOI	MAOI No inhibition of cytochrome P450

Mood Stabilizers

General Prescribing Information

- examples: lithium, divalproex, lamotrigine, carbamazepine
- used mainly for long-term stabilization of bipolar disorder, also used as first-line monotherapy or in conjunction with atypical antipsychotics for acute episodes of bipolar disorder (i.e. depression and mania)
- vary in their ability to "treat" (i.e. reduce symptoms acutely) or "stabilize" (i.e. prevent relapse and recurrence) manic and depressive symptoms; multi-agent therapy can be avoided in many patients but it is common
- before initiating, get baseline: CBC with differential and platelets, ECG (if patient >45 y/o or cardiovascular risk), BUN, creatinine, extended electrolytes, TSH, LFTs for divalproex and carbamazepine
- screening for: pregnancy, thyroid, neurological, renal, liver, cardiovascular diseases
- full effects may take 2-4 wk, thus may need acute coverage with benzodiazepines or antipsychotics

Specific Prescribing Information

- detailed pharmacological guidelines available online from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)
- for clinical information for treating bipolar disorder (see *Mood Disorders, PS10*)
- be mindful that divalproex and carbamazepine are teratogenic thus if prescribed for women at reproductive age, a reliable contraceptive strategy is required

Table 20. Commonly Used Mood Stabilizers

	Lithium	Lamotrigine (Lamictal®)	Divalproex (Epival®)	Carbamazepine (Tegretol®)
Indications	**1st line** Acute mania (monotherapy or with adjunct SGA) Bipolar I depression (monotherapy or in combination with divalproex, SSRI, or bupropion) Bipolar disorder maintenance (monotherapy or with adjunct SGA) **Other uses** Bipolar II depression Augmentation of antidepressants in MDD and OCD Schizoaffective disorder Chronic aggression, antisocial behaviour Recurrent depression	**1st line** Bipolar I depression (monotherapy) Bipolar disorder maintenance (limited efficacy in preventing mania, more effective when combined with lithium) **Other uses** Bipolar II depression Not recommended for acute mania	**1st line** Acute mania (monotherapy or with adjunct SGA) Bipolar I depression (combination with lithium or SSRI) Bipolar disorder maintenance (monotherapy or with adjunct SGA) **Other uses** Bipolar II depression Rapid cycling bipolar disorder Mixed phase/dysphoric mania	**2nd line** Acute mania (monotherapy) Bipolar disorder maintenance (monotherapy or in combination with lithium) **Other uses** Rapid cycling bipolar disorder
Mode of Action	Unknown Therapeutic response within 7-14 d	May inhibit 5-HT3 receptors May potentiate DA activity	Depresses synaptic transmission Raises seizure threshold	Depresses synaptic transmission Raises seizure threshold
Dosage	Adult: 600-1500 mg/d Geriatric: 150-600 mg/d Usually daily dosing Blood levels monitored and dose adjusted accordingly	Note: very slow titration required due to risk of Stevens-Johnson Syndrome Dose adjusted in patients taking other anticonvulsants such as divalproex Daily dose: 100-200 mg/d	750-2500 mg/d Usually daily dosing with ER preparation	400-1600 mg/d Usually BID or TID dosing
Therapeutic Level	Adult: 0.8-1.0 mmol/L (1.0-1.25 mmol/L for acute mania) Geriatric: 0.6-0.8 mmol/L	Therapeutic plasma level not established Dosing based on therapeutic response	17-50 mmol/L Same therapeutic levels as used for seizure prophylaxis (no data specific for mood stabilizing effect)	350-700 µmol/L Same therapeutic levels as used for seizure prophylaxis (no data specific for mood stabilizing effect)
Monitoring	Monitor serum levels every 5-7 d until therapeutic (always 12 h after dose) Then monitor monthly, then q2-3 mo Monitor thyroid function, creatinine q6 mo	Monitor for skin rash and suicidality when initiating treatment	Monitor serum levels every 5-7 d until therapeutic LFTs weekly x 1 mo, then monthly, then q2-3 mo due to risk of liver dysfunction Watch for signs of liver dysfunction: nausea, edema, malaise Check platelets and monitor levels to adjust dosage and confirm adherence	Monitor serum levels every 5-7 d until therapeutic Weekly blood counts for 1st mo, due to risk of agranulocytosis Watch for signs of blood dyscrasias: fever, rash, sore throat, easy bruising
Side Effects	GI: N/V, diarrhea, stomach pain GU: polyuria, polydipsia, nephrogenic diabetic insipidus, glomerulonephritis, renal failure, decreased glomerular filtration rate CNS: fine tremor, headache, fatigue, lethargy Hematologic: reversible benign leukocytosis Other: teratogenic (Ebstein's anomaly), hypothyroidism, weight gain, edema, worsening of psoriasis, bradycardia, ECG changes	Skin: rash (consider discontinuing due to risk of Steven-Johnson syndrome which is an emergency), slow dose titration to reduce risk Otherwise, usually well tolerated (GI: N/V, diarrhea CNS: ataxia, dizziness, diplopia, headache, somnolence Other: anxiety)	GI: liver dysfunction, N/V, diarrhea CNS: ataxia, drowsiness, tremor, sedation, cognitive blurring Other: hair loss, weight gain, thrombocytopenia, neural tube defects when used in pregnancy, polycystic ovarian syndrome	GI: N/V, diarrhea, hepatic toxicity CNS: ataxia, dizziness, slurred speech, drowsiness, confusion, nystagmus, diplopia Hematologic: transient leukopenia (10%), rare agranulocytosis, aplastic anemia Skin: rash (5% risk; consider discontinuing drug because of risk of Stevens-Johnson syndrome) Other: neural tube defects when used in pregnancy
Interactions	NSAIDs, thiazides, ACEI, and metronidazole decrease clearance, risk for lithium toxicity		OCP	OCP

Lithium Toxicity

- clinical diagnosis as toxicity can occur at therapeutic levels
- common causes: overdose, sodium/fluid loss, concurrent medical illness or initiation of NSAIDs, steroids, diuretics, or ACEI
- **clinical features**
  - GI: severe nausea/vomiting and diarrhea
  - cerebellar: ataxia, slurred speech, lack of coordination
  - cerebral: drowsiness, myoclonus, tremor, upper motor neuron signs, seizures, delirium, coma
- **management**
  - discontinue lithium for several days and begin again at a lower dose when lithium level has fallen to a non-toxic range
  - monitor serum lithium levels, creatinine, BUN, electrolytes
  - IV saline
  - hemodialysis if lithium >2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 h, or deterioration

Long-term lithium use can lead to a nephropathy and diabetes insipidus in some patients

Anxiolytics

- anxiolytics decrease anxiety regardless of the cause; they can mask or alleviate symptoms
- **indications**
  - short-term treatment of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders, agitation or aggression associated with acute mania, or psychosis; any other circumstance with the goal of decreasing anxiety
- **relative contraindications**
  - major depression (except as an adjunct to other treatment), history of drug/alcohol misuse, caution in pregnancy/breastfeeding
  - myasthenia gravis is a relative contraindication for benzodiazepines
  - risk of falls
- **mechanism of action**
  - benzodiazepines: potentiate binding of GABA to its receptors; results in decreased neuronal activity
  - buspirone: partial agonist of 5-HT1A receptors

Benzodiazepine Antagonist – Flumazenil (Anexate®)
Use for suspected benzodiazepine overdose
Specific antagonist at the benzodiazepine receptor site

Benzodiazepines

- should be used for limited periods (i.e. days-weeks) to avoid tolerance and dependence
- all benzodiazepines are sedating, decrease respiratory drive, and increase risk for falls, confusion, and motor vehicle accidents; be wary with use in the elderly, especially in combination with other psychotropic medications
- have similar efficacy, so choice depends on half-life, metabolites, and route or schedule of administration
- taper slowly over weeks-months because they can cause withdrawal reactions (see below)
- beware of use with alcohol and other CNS depressants because of potentiation of CNS depression; caution with drinking and driving/machinery use
- **side effects**
  - CNS: drowsiness, cognitive impairment, reduced motor coordination (falls), memory impairment
  - dependence, tolerance, withdrawal
- **withdrawal**
  - low dose withdrawal symptoms: tachycardia, HTN, panic, rebound insomnia, anxiety, impaired memory and concentration, perceptual disturbances
  - high dose or rapid withdrawal symptoms: hyperpyrexia, seizures, death
  - onset: 1-2 d (short-acting), 2-4 d (long-acting)
  - duration: days-weeks
  - complication with above 50 mg diazepam/d or abrupt withdrawal: autonomic hyperactivity, seizures, delirium, arrhythmias
  - management: taper slowly; may need to switch to a long-acting benzodiazepine
  - similar to but less severe than alcohol withdrawal; can be fatal
- **overdose**
  - overdose is common but rarely fatal unless combined with other substances
  - more dangerous or potentially fatal when combined with alcohol, other CNS depressants, opioids, or TCAs

Benzodiazepines That are Safe for Patients with Impaired Liver Function

LOT
Lorazepam
Oxazepam
Temazepam

Buspirone (Buspar®)

- primary use: GAD
- may be preferred over benzodiazepines because it is non-sedating, has no interaction with alcohol, does not alter seizure threshold, not prone to abuse
- onset of action: 2 wk
- side effects: dizziness, drowsiness, nausea, headache, nervousness, EPS

Z-drugs for Sleep

- non-benzodiazepine sedatives indicated for short-term management of insomnia
- examples include zopiclone (Imovane®), eszopiclone (Lunesta®), and zolpidem (Sublinox®)
- anecdotally provide a more restful sleep than benzodiazepines
- similar side effect profile and warnings to benzodiazepines
- should not be used long-term due to side effects and likelihood of dependency

Table 21. Dosing and Indications for Common Anxiolytics

Class	Drug	Dose Range (mg/d)	$t_{1/2}$ (h)	tmax (h)	Appropriate Use
Benzodiazepines					
Long-acting	Clonazepam (Rivotril®)	0.25-4	18-50	1-4	Seizure prevention, akathisia, generalized anxiety disorder, panic disorder
	Diazepam (Valium®)	2-40	30-100	1-2	Seizure prevention, muscle relaxant, alcohol withdrawal, generalized anxiety
	Chlordiazepoxide (Librium®)	5-300	30-100	1-4	Alcohol withdrawal
	Flurazepam (Dalmane®)	15-30	50-160	0.5-1	Should be avoided
Short-acting	Alprazolam (Xanax®)	0.25-4.0	6-20	1-2	Should be avoided due to high dependency rate
	Lorazepam (Ativan®)	0.5-6.0	10-20	1-4	Alcohol withdrawal (no first-pass liver metabolism), akathisia, short-term sedation for anxiety during procedures (e.g. CT or MRI), generalized anxiety; sublingual or IM for rapid action
	Oxazepam (Serax®)	10-120	8-12	2-3	Alcohol withdrawal (no first-pass liver metabolism), generalized anxiety disorder
	Temazepam (Restoril®)	7.5-30	8-20	2-5	Should be avoided
	Triazolam (Halcion®)	0.125-0.5	1.5-5	1-2	Shortest $t_{1/2}$, rapid sleep without daytime sedation (e.g. overnight plane travel), but risk of rebound insomnia
Azapirones					
	Buspirone (Buspar®)	15-30	2-3	1-1.5	Generalized anxiety disorder

Somatic Therapies

Electroconvulsive Therapy

- the fastest and most effective acute treatment of depression
- ECT is a safe and controlled way of producing seizures to treat mental illness
- various methodological improvements have been made since the first treatment in 1938 to reduce adverse effects
- modern ECT: induction of a generalized seizure using an electrical pulse through scalp electrodes while the patient is under general anesthesia with a muscle relaxant
- considerations: unilateral vs. bilateral electrode placement, pulse rate, energy, number, and spacing of treatments
- usual course is 6-12 treatments, 2-3 treatments per wk
- indications
  - treatment-resistant depression (unipolar, bipolar I, bipolar II): psychotic features, catatonic features, when medications may be unsafe or rapid response is needed (e.g. cachexia, severe dehydration, frail elderly, high suicide risk, pregnancy)
  - catatonia: refractory, severe, or life-threatening
  - schizophrenia: treatment-resistant, acute symptoms, catatonia, history of NMS
  - mania: refractory, severe or life-threatening situation
  - personal or family history of good response to ECT
  - inconclusive evidence for OCD
- adverse effects: risk of anesthesia (equal to risk of ECT), memory loss (may be retrograde and/or anterograde, tends to resolve by 6-9 mo, permanent impairment controversial), transient headaches, transient myalgias
- unilateral ECT causes less memory loss than bilateral but may not be as effective
- contraindications: no absolute contraindications; relative contraindications: increased intracranial pressure, recent (<4 wk) hemorrhagic stroke, recent (<2 wk) MI, requires special monitoring

ECT in Society
Prior to the 1940's, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by negative depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients with severe mental illness, including depression

Electroconvulsive Therapy for Treatment Resistant Schizophrenia
Cochrane DB Syst Rev 2019;CD011847
Purpose: Assess benefits and harms of ECT for people with treatment-resistant schizophrenia.
Outcomes: Moderate-quality evidence indicates that relative to standard care, ECT has a positive effect on medium-term clinical response for people with treatment-resistant schizophrenia. However, there is no clear and convincing advantage or disadvantage for adding ECT to standard care for other outcomes.

Repetitive Transcranial Magnetic Stimulation (rTMS)

- noninvasive production of focal electrical currents in select brain circuits using magnetic induction
- indications: strong evidence for treatment-resistant depression and pain disorders; possibly efficacious for anxiety disorders, PTSD, eating disorders, and substance use disorders; not as effective as ECT for depression
- adverse effects: common – transient local discomfort, hearing issues, or cognitive changes; rare – seizure, syncope, mania induction

Magnetic Seizure Therapy (Experimental)

- magnetic seizure therapy (MST) is generalized seizure induction using strong magnetic current
- early studies demonstrate efficacy for depression as well as anxiety, with reduced memory effects vs. ECT

Neurosurgical Treatments

Ablative/Lesion Procedures

- used for MDD or OCD unresponsive to all other forms of treatment; efficacy ranges from 25-75% depending on procedure
- adverse effects: related to lesion location and size, high-risk of suicide in those who are not helped by surgery
- focused ultrasound therapy (FUS) is an experimental surgical technique under investigation for the treatment of MDD, OCD with the advantage of avoiding an open skull surgery

Deep Brain Stimulation (Experimental)

- placement of small electrode leads in specific brain areas to alter neuronal signaling
- most evidence for treating OCD, some evidence for other disorders such as treatment-resistant MDD
- response rates (>50% symptom reduction) of 40-70%, adverse effects related to surgical risks and poor treatment response

Vagus Nerve Stimulation

- direct, intermittent electrical stimulation of left cervical vagus nerve via implanted pulse generator
- used for chronic, recurrent MDD with poor response to previous therapy and ECT
- slow onset, approximately 30% response rate at 1 yr

Other Therapy Modalities

Phototherapy (Light Box Therapy)

- bright light source exposure (usually 10000 lux) for 30 min daily within the first hour of awakening
- proposed mechanisms: reverses pathological alterations in circadian rhythm through action on suprachiasmatic nucleus
- indications: seasonal affective disorder (SAD), non-seasonal depression (as augmentation), and some sleep disorders
- adverse effects: mania induction, reaction with photosensitizing drug or photosensitive eye or skin conditions

Aerobic Exercise

- moderate-intense aerobic exercise is associated with acute increased release of serotonin, phenethylamine, brain-derived neurotrophic factor, endogenous opioids, and cannabinoids (likely this combination is what contributes to the "runner's high")
- associated with long term increases in grey matter in multiple areas, as well as improvements in cognition, memory, and stress tolerance
- indications: monotherapy for mild-moderate MDD; adjunctive therapy for moderate-severe MDD
- may be helpful in PTSD, schizophrenia

Canadian Legal Issues

Common Forms

- the legislation is specific to each province, as are the types and numbers of forms, but the principles are common across Canada

Table 22. Common Forms Under the Mental Health Act (in Ontario)

Form	Who Signs	When	Expiration Date	Right of Patient to Review Board Hearing	Options Before Form Expires
Form 1: Application by physician to bring a patient to hospital (schedule 1 facility) for psychiatric assessment against patient's will (Form 42 given to patient)	Any physician	Within 7 d after having examined the patient	72 h after hospitalization Void if not implemented within 7 d	No	Form 3 and 30 or voluntary admission or send home ± follow-up
Form 2: Order by Justice of the Peace to bring patient to a hospital for an examination against patient's will	Justice of the Peace	No statutory time restriction	7 d from when completed Purpose of form is complete once patient brought to hospital	No	Form 1 and 42 or voluntary admission or send home ± follow-up
Form 3: Certificate of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)	Any physician other than physician who completed Form 1	Before expiration of Form 1 Any time to change status of a voluntary inpatient	14 d	Yes	Form 4 and 30 or voluntary admission (Form 5)
Form 4: Certificate of renewal of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)	Any physician, usually the attending physician following patient on Form 3	Prior to expiration of Form 3	First: 1 mo Second: 2 mo Third: 3 mo (max)	Yes	Form 4 and 30 or voluntary admission (Form 5)
Form 4a: Certificate of continuation of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor, Form 17 sent to the Capacity and Consent Board, copies to chart)	Any physician, usually the attending physician following patient on Form 4	Prior to expiration of the third Form 4	3 mo	Mandatory review board hearing	Another Form 4a or voluntary admission
Form 5: Change to informal/voluntary status	Any physician, usually the attending physician following patient on Form 3/4/4a	Whenever deemed appropriate (i.e. the criteria for involuntary admission under the Mental Health Act are no longer fulfilled)	N/A	N/A	N/A
Form 30: Notice to patient that patient is now under involuntary admission on either Form 3, 4, or 4a (original to patient, copy to chart)	Physician issuing the Form 3/4/4a	Whenever Form 3/4/4a filled	N/A	Yes	N/A
Form 33: Notice to patient that patient is incapable of consenting to treatment of a mental disorder, and/or management of property and/or disclosure of health information (original to patient, notice to rights advisor, copy to chart)	Attending physician	Whenever deemed appropriate	N/A	Yes	N/A
Form 42: Notice to the patient that patient is now on a Form 1 and the reason for this change (original to patient, copy to chart)	Physician who is signing Form 1	Whenever Form 1 filled	N/A	No	

* Schedule 1 Facilities: Able to provide intensive inpatient and outpatient care

Form 1: Application for Psychiatric Assessment

- Filled out when patients are thought to be in imminent danger to harm themselves (suicide) or others (homicide), or when they are incapable of self-care (e.g. not dressed for freezing weather) and are suffering from an apparent mental disorder
- Based on any combination of the physician's own observations and facts communicated by others
- Box A or Box B completed
- **Box A**: Serious Harm Test
- The Past/Present Test assesses current behaviours/threats/attempts
- The Future Test assesses the likelihood of serious harm occurring as a result of the presenting mental disorder. In this section, one should document evidence of the mental disorder and concerning behaviours/thoughts
- **Box B**: Patients with a known mental disorder who are incapable of consenting to treatment (substitute decision-maker needed), have previously received treatment and improved, and are currently at risk of serious harm due to the same mental disorder

Consent

- see Ethical, Legal, and Organizational Medicine, ELOM12

Community Treatment Order (CTO)

- purpose: a community treatment order (CTO) orders a person suffering from a serious mental disorder to receive treatment and supervision in the community. Based on a comprehensive plan outlining medications, appointments, and other care believed necessary to allow the person to live in the community (vs. in a psychiatric facility, where conditions are more restrictive)
- intended for those who:
  - due to their serious mental disorder, experience a pattern of admission to a psychiatric facility where condition is usually stabilized
  - after being released, these patients often stop treatment, leading to destabilization
  - due to the destabilization of their condition, these patients usually require readmission to hospital
  - if CTO violated (i.e. treatment not taken, does not comply with follow up), the physician can issue a Form 47 which is an order for examination that allows the police to bring the patient to the hospital for an examination (usually the patient is examined and the treatment will continue as per the CTO)
- criteria for a physician to issue a CTO
  - patient with a prior history of psychiatric hospitalization (cumulative ≥30 d over ≥2 hospitalizations in the past 3 yr), or the person has been subject to a previous CTO in the past 3 yr
  - a community treatment plan for the person has been made
  - examination by a physician within the previous 72 h before entering into the CTO plan
  - ability of the person subject to the CTO to comply with it
  - consultation with a rights advisor and consent of the person or the person's substitute decision maker
- CTOs are valid for 6 mo unless they are renewed or terminated at an earlier date such as
  - when the person or his/her substitute decision-maker withdraws consent to the community treatment plan
- CTO process is consent-based and all statutory protections governing informed consent apply
- the rights of a person subject to a CTO include
  - the right to a review by the Consent and Capacity Board with appeal to the courts each time a CTO is issued or renewed
  - a mandatory review by the Consent and Capacity Board every second time a CTO is renewed
  - the right to request a re-examination by the issuing physician to determine if the CTO is still necessary for the person to live in the community
  - the right to review findings of incapacity to consent to treatment
  - provisions for rights advice

CTO Legislature

Ontario passed CTO legislature on December 1, 2000 (known as "Brian's Law")

Similar CTOs have been implemented in Saskatchewan (1995), Manitoba (1997), and British Columbia (1999)

Duty to Inform/Warn

- see Ethical, Legal, and Organizational Medicine, ELOM11

Landmark Psychiatry Clinical Trials

Trial	Reference	Results
Schizophrenia		
CATIE	NEJM 2005;353:1209-1223	**Title**: Title:Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia **Purpose**: Compare the effectiveness of a proxy first-generation antipsychotic (perphenazine) to several second-generation antipsychotics. **Methods**: 1460 patients with chronic schizophrenia were randomly assigned in a double-blind study to receive one of perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone for up to 18 mo. **Results**: Perphenazine did not differ significantly in overall effectiveness or benefits compared to the second-generation antipsychotics. Perphenazine was the most cost-effective drug. Individual clinical circumstances impacted drug effectiveness. Patients who have a poor response to an initial medication may tolerate and see greater effectiveness with a different medication. **Conclusions**: First and second-generation antipsychotics did not differ in overall effectiveness. Patient factors must be considered when prescribing antipsychotic medications.
Bipolar Disorder		
STEP-BD	NEJM 2007;356(17):1711-1722	**Title**: Effectiveness of Adjunctive Antidepressant Treatment for Bipolar Depression **Purpose**: To determine the effectiveness and safety of standard antidepressant agents for depressive episodes associated with bipolar disorder (bipolar depression) **Methods**: Patients with bipolar depression were randomly assigned to receive a mood stabilizer (MS) with placebo (n=187) or with paroxetine or bupropion (n=179) for 26 wk. The primary outcome was recovery, defined as 8 consecutive weeks of euthymia. **Results**: There was no significant difference in recovery between the two groups (23.5% vs. 27.3%; p=0.40). Patients in the MS group with placebo demonstrated nonsignificant superiority on secondary outcome measures. **Conclusions**: In combination with MS, standard antidepressants were not associated with increased efficacy or increased risk of treatment-emergent affective switch.

Trial	Reference	Results
Major Depressive Disorder		
TRANSFORM-2	Am J Psychiatry 2019,176(6):428-438	**Title**: Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined with a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study **Purpose**: Evaluate the efficacy and safety of flexibly dosed esketamine nasal spray for patients with treatment-resistant depression. **Methods**: Patients with treatment-resistant depression were randomly assigned treatment of esketamine nasal spray with a newly initiated antidepressant or a placebo nasal spray with a newly initiated antidepressant. **Results**: 197 participants completed the study. Patients receiving the esketamine nasal spray plus antidepressant treatment demonstrated a change in Montgomery-Åsberg Depression Rating Scale score that was significantly greater than placebo nasal spray plus antidepressant at d 28. Clinically meaningful improvements were found in the esketamine group earlier in the study timeline. **Conclusions**: Esketamine nasal spray was a safe, rapid-acting, and efficacious therapy for treatment-resistant depression.
STAR*D	Am J Psychiatry 2006;163:1905-1917	**Title**: Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report **Purpose**: To determine the acute and longer-term effectiveness of depression treatments in primary and speciality care settings. **Methods**: Patients with non-psychotic MDD received one (n=3671) to four (N=123) successive acute treatment steps (steps consisted of medication ± psychotherapy). Patients were encouraged to move to the next step if not achieving remission or unable to tolerate treatment. **Results**: Remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively. The overall cumulative remission rate was 67%. Patients requiring more treatment steps had higher relapse rates during the naturalistic follow-up phase. **Conclusions**: Patients with persistent MDD benefit from trying successive treatment steps, but remission of depression decreases with additional treatment strategies.
TADS	JAMA 2004;292:807-820	**Title**: Fluoxetine, Cognitive-Behavioural Therapy and Their Combination for Adolescents with Depression: Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial **Purpose**: To evaluate effectiveness of fluoxetine, cognitive behavioral therapy (CBT), CBT with fluoxetine, and placebo among adolescents with major depressive disorder (MDD). **Methods**: RCT at 13 US academic and community clinics between 2000-2003. 12-17 yr old patients with a primary DSM IV diagnosis of MDD assigned to one of the aforementioned four treatment arms. The primary outcome was the Children's Depression Rating Scale- Revised (CDRSR) total score. **Results**: Fluoxetine with CBT had a statistically significant CDRSR score as compared to placebo (P=0.001) with a 71% response rate. This combination was greater than fluoxetine alone (P=0.02), and CBT alone (P=0.01). Fluoxetine alone was greater than CBT alone (P=0.01). **Conclusion**: Combination of fluoxetine with CBT offered the most favorable benefit-risk tradeoff for adolescents with MDD.
Alcohol Dependence		
COMBINE	JAMA 2006;295(17):2003-2017	**Title**: Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence: A Randomized Controlled Trial **Purpose**: To evaluate the efficacy of medication, behavioral therapies, and their combinations for treatment of alcohol dependence. **Methods**: Patients (n=1383) received medical management with 16 wk of naltrexone (100 mg/d) or acamprosate (3 g/d), both, and/or placebos with or without combined behavioral intervention (CBI), and were evaluated for up to 1 yr after treatment. **Results**: Patients receiving naltrexone plus medical management, CBI plus medical management and placebos, or both naltrexone and CBI plus medical management had higher percent days abstinent than those receiving placebos and medical management. Acamprosate showed no significant effect on drinking vs placebo, either by itself or with any combination of naltrexone, CBI, or both. Conclusions: Patients receiving medical management with naltrexone, CBI, or both, fared better on drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI. No combination produced better efficacy than naltrexone or CBI alone in the presence of medical management.

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PH Public Health and Preventive Medicine

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Acronyms

ADLs	activities of daily living	FP	false positives	NNT	number needed to treat	SARS	severe acute respiratory syndrome
AR	attributable risk	FN	false negatives	NPV	negative predictive value	SDOH	social determinants of health
CAS	Children's Aid Society	FOBT	fecal occult blood test	OR	odds ratio	SDS	safety data sheets
CBA	cost benefit analysis	IMR	infant mortality ratio	PFT	pulmonary function test	SMR	standardized mortality ratio
CEA	cost effectiveness analysis	ITT	intention-to-treat analysis	PHAC	Public Health Agency of Canada	TP	true positives
CFR	case fatality rate	LICO	low income cut-off	PP	per protocol analysis	TN	true negatives
CTFPHC	Canadian Task Force on Preventive Health Care	MERS	Middle East respiratory syndrome	PPV	positive predictive value	WHMIS	Workplace Hazardous Materials Information System
DALY	disability adjusted life year	MHO	Medical Health Officer	PSA	prostate screening antigen	WHO	World Health Organization
DDT	dichlorodiphenyltrichloroethane	MOH	Medical Officer of Health	PYLL	potential years of life lost	WSIB	Workplace Safety and Insurance Board
EBM	evidence-based medicine	MMR	maternal mortality ratio	QALY	quality adjusted life year		
		NNH	number needed to harm	QI	quality improvement		
				RR	relative risk		

Public Health Context

- see Ethical, Legal, and Organizational Medicine, *Overview of Canadian Healthcare System*, ELOM2 for the organization of health care in Canada including the legal foundation and historical context

Definitions

- population health
  - refers to the health of defined groups of people, their health determinants, trends in health, and health inequalities
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; access to and quality of healthcare services
  - broader scope compared to public health; accounts for socioeconomic, policy, and historical issues
- public health
  - an organized effort by society to promote, protect, improve, and when necessary, restore the health of individuals, specified groups, or the entire population
  - a combination of sciences, skills, and values that function through collective societal activities and involve programs, services, and institutions aimed at protecting and improving the health of the population as a whole
  - public health services in many provinces (e.g. Ontario) are administered, funded, and delivered entirely separately from healthcare services
- epidemiology
  - the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems
- Public Health and Preventive Medicine (formerly called Community Medicine)
  - the medical specialty that focuses on population rather than individuals' health
  - works with diverse populations to improve population health, address SDOH, and promote health equity
  - 5 year Royal College training in medical skills and knowledge, epidemiology, statistics, social sciences, public administration, policy development, program management, and leadership

Sources: Shah, CP. Chapter 2 Measurement and Investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
Shah, CP. Chapter 15 Community Health Services. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
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Preparing for the LMCC
The AFMC Primer on Population Health is the core text for the LMCC and is available as an online resource on the AFMC website (http://phprimer.afmc.ca) For the LMCC exam, it is recommended that you also read Chapter 15 in Shah CP. Public health and preventive medicine in Canada, 5th ed. Toronto: Elsevier, 2003

Historical Perspective
Over the last century, the focus of public health has evolved:
Infectious diseases: a prominent issue in low- and middle-income countries and higher income countries alike; includes emergent diseases caused by unfamiliar or new pathogens, inefficient or inappropriate antibiotic use, travel, global warming (e.g. HIV, drug-resistant TB, COVID-19), and the manufactured conditions of crisis and/or routine conditions of poverty imposed on Indigenous, Black, and other communities of colour
Chronic diseases: have increased morbidity and mortality (e.g. heart disease and cancer due to risk factors and/or exposures) and disproportionately affect Indigenous populations throughout the world
Social determinants of health: driven by a growing body of evidence since the 1980s that universal access to health care services did not ameliorate health inequalities, and that significant improvements in health could only be achieved by going 'upstream' with action on policies

Public Health in Canada

The public health service in Canada is composed of various agencies at the federal (Public Health Agency of Canada), provincial (e.g. Public Health Ontario), and municipal/local levels (local public health units). The organization of the public health system in each province varies widely and is usually separate from the healthcare system.

Mission of the Public Health Agency of Canada (federal only): to promote and protect the health of Canadians through leadership, partnership, innovation, preparedness, and action in public health

- local public health units and services within regional health authorities (in most provinces except Ontario, where local public health units are either autonomous or within local government) provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range widely (hundreds to millions), covering areas of 15-1.5 million km ^{2}
- the "core functions" of public health include six essential activities

The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC Primer on Population Health [Internet]. The organization of health services in Canada; [cited 2006 Mar 25]. Available from https://phprimer.afmc.ca/en/

1. health protection: measures taken to address potential health risks at the population level through regulation and advising government (e.g. safe water and food supply)
2. health surveillance: monitoring and predicting health outcomes and determinants with systematic, longitudinal data collection
3. disease and injury prevention: addressing infectious disease through preventive (e.g. vaccination, clinical infection prevention and control practices such as contact, droplet, airborne precautions) and control (e.g. quarantine) measures; reducing morbidity through lifestyle improvement

Example of a Municipal Health Unit: The Middlesex-London Health Unit
Serves 450000 people living, working, visiting, and studying in the city of London and Middlesex county
275 full-time staff including MOHs (physicians), public health nurses, epidemiologists, health promotion educators, dental hygiene managers, etc.
Services include infectious disease control, ensuring environmental health standards, health promotion, and providing family health programs

4. population health assessment: studying and engaging with a community to understand their needs and improve policies and services
5. health promotion: advocating for improved health through broad community and government measures (e.g. policy, interventions, community organizations)
6. emergency preparedness and response: developing protocols and infrastructure for natural (e.g. hurricane) and man-made (e.g. opioid crisis) disasters. In many types of health-related disasters, public health leads/provides leadership on the disaster response

Sources: Shah, CP. Chapter 15 Community Health Services. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC Primer on Population Health [Internet]. The organization of health services in Canada; [cited 2006 Mar 25]. Available from https://phprimer.afmc.ca/en/

Legislation and Public Health in Canada

Table 1. Legislation and Public Health in Canada

Federal	Provincial	Municipal (Ontario)
Health Canada • Provides health services to the Canadian military and veterans • Provides non-insured health benefits (NIHB) to status First Nations peoples and Inuit, and is responsible for the funding of healthcare services on reserve • Approves new drugs and medical devices • Food Guide **Public Health Agency of Canada** (main Government of Canada agency responsible for public health) • An independent body created post-SARS to strengthen public health capacity and response • Focuses on preventing chronic diseases, preventing injuries, and responding to public health emergencies and infectious disease outbreaks • Activities include CTFPHC guideline secretariat, knowledge brokers • Oversees immigration screening, protects Canadian borders (e.g. airport health inspection) • Liaises with the WHO on global health issues **Canadian Food Inspection Agency** • Regulates food labeling • Deals with animal-related infections **Canadian Institutes of Health Research (CIHR)** • Formed in 2000 to support research to improve health and the health care system	Each province has its own Public Health Act or equivalent (e.g. the *Health Protection and Promotion Act* in Ontario) and agencies (e.g. Public Health Ontario) • Designates the creation of geographic areas for the provision of public health services • Gives powers to the Chief Medical Officer of Health to control public health hazards • Specifies diseases to be reported to public health units by physicians, laboratories, and hospitals (see *Appendix, PH31*) • Mandates programs that address public health issues, environmental health, and chronic disease prevention	Local public health units (e.g. Middlesex-London Health Unit) deliver programs mandated by provincial, municipal, or regional legislation and are responsible for the delivery of most public health services, such as: • Infectious disease control, including the follow-up of reported diseases and management of local outbreaks • Inspection of food premises, including those in hospitals, nursing homes, and restaurants • Family health services, including pre-conception, preschool, school-aged, and adult health programs • Tobacco control legislation enforcement • Assessment and management of local environmental health risks • Collection and dissemination of local health status reports • Oral health • By-laws may be approved by municipal governments to facilitate public health issues

WHO Updates To Essential Public Health Functions

The WHO updated the essential public health functions to better address 21st century health challenges:

1. Monitor and evaluate the population's health status, health service utilization and surveillance of risk factors and threats to health
2. Public health emergency management
3. Assure effective public health governance, regulation and legislation
4. Support efficient and effective health systems and multisectoral planning, financing and management for population health
5. Protect populations against health threats, including environment and occupational hazards, communicable disease threats, food safety, chemical and radiation hazards
6. Promote prevention and early detection of diseases
7. Promote health and well-being and actions to address the wider determinants of health and inequity
8. Ensure community engagement, participation and social mobilization for health and well-being
9. Ensure adequate quantity and quality of public health workforce
10. Assure quality of and access to health services
11. Advance public health research
12. Ensure equitable access to and rational use of essential medicines and other health technologies

Source: WHO. 21st century health challenges: can the essential public health functions make a difference? 2021. Available from:https://www.who.int/publications/i/item/9789240038929

Chief Public Health Officer (CPHO) of Canada

Responsible for the Public Health Agency of Canada (PHAC) and reports to the Minister of Health

As the federal government's lead public health professional, provides advice to the Minister of Health and Government of Canada and collaborates with other governments, jurisdictions, agencies, organizations, and countries on health matters

Communicates public health information to health professionals, stakeholders, and the public

In an emergency, such as an outbreak or natural disaster, directs PHAC staff, including medical professionals, scientists, and epidemiologists, to coordinate emergency response

Source: Government of Canada: the role of the chief public health officer [Internet]. Government of Canada; [updated 2016 Feb 8; cited 2022 July]; [about two screens]. Available from: https://www.canada.ca/en/public-health/corporate/organizational-structure/canada-chief-public-health-officer/role-chief-public-health-officer.html

Determinants of Health

Concepts of Health

- **wellness**: "state of dynamic physical, mental, social, and spiritual well-being that enables a person to achieve full potential and have an enjoyable life"
- **disease**: "abnormal, medically-defined changes in the structure or function of the human body"
- **illness**: "an individual's experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles"
- **illness behaviour**: an individual's actions resulting from and responding to their illness, including their interactions with, or avoidance of, the healthcare system
- **sickness**: views the individual and their society hold towards a health condition, affecting their thoughts and actions
- **impairment**: "any loss or abnormality of psychological, physiological, or anatomical structure or function"
- **disability**: "any restriction or lack of ability to perform an activity within the range considered normal for a human being"
- **handicap**: a disadvantage for an individual arising from impairment or disability
  - "limits or prevents the fulfillment of an individual's normal role as determined by society and depends on age, sex, social, and cultural factors"
- **health equity**: when all people have "the opportunity to attain their full health potential" and no one is "disadvantaged from achieving this potential because of their social position or other socially determined circumstance." Health inequities are systematic differences in the health of individuals/groups which are considered unjust

- **health equality**: defined as where populations have equal or similar health status. Health inequalities are systematic differences in the health of groups that do not necessarily carry a moral judgement
- **health intersectionality**: refers to the concept that an individual's various social identities (e.g., race, weight, sex, class, ability etc.) can combine and overlap to create unique experiences of health discrimination and/or privilege.
- **health stigma**: refers to the reduction of a person's identity to negative stereotypes about their health status (e.g. weight stigma). Stigma may limit patient trust, healthcare quality, and accessibility

Source: ACC Institute of Human Services, Special Needs Education. Impairment, Disability, and Handicap: what's the difference? [Internet]. Institute of Human Services; 2018 Nov 9 [cited 2020 Apr 28]. Available from: https://acc.edu.sg/en/impairment-disability-and-handicap-whats-the-difference/

Determinants of Health

- 1974: the Honourable Marc Lalonde, federal Minister of Health, publishes A New Perspective on the Health of Canadians which outlines four factors that determine health: "human biology, environment, lifestyle, and health care organizations." The idea of determinants of health has since been expanded and refined to include many additional factors
- 2023: per the WHO, the SDOH are "non-medical factors that influence health outcomes", including "the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life"

Sources: Shah, CP. Concepts, Determinants, and Promotion of Health. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC primer on population health [Internet]. Chapter 1, Concepts of health and illness [cited Jul 2022]; [about 7 p.]. Available fromhttps://phprimer.afmc.ca/en/part-i/chapter-1/
World Health Organization: Health topics [Internet]. Social Determinants of Health [cited Jun 2023]. Available from: https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1

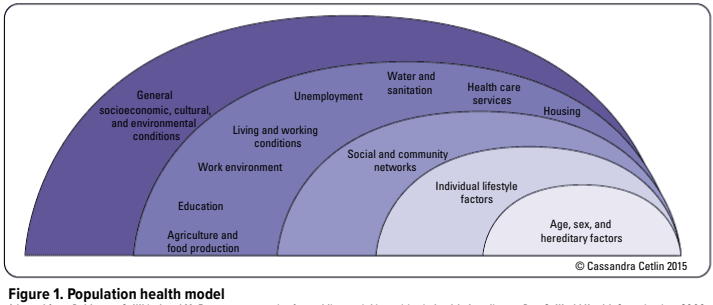


Figure 1. Population health model
Adapted from Dahlgreen G, Whitehead M. European strategies for tackling social inequities in health: Leveling up Part 2. World Health Organization, 2006

- **cultural humility**: an approach to health care based on humble acknowledgement of oneself as a learner when it comes to understanding a person's experience. This is a life-long process of learning and being self-reflexive
- **cultural safety**:
  - developed by Dr. Irihapeti Ramsden, a Maori nurse scientist, in the 1980s and is "concerned with the power relationships between nurses and those in their care. The recipients of nursing care are empowered to decide what is culturally safe rather than complying passively with the authority of nurses or other health professionals" - Cancer Australia
  - "an approach that considers how social and historical contexts, as well as structural and interpersonal power imbalances, shape health and health care experiences. Practitioners are self-reflective/self-aware with regards to their position of power and the impact of this role in relation to patients" - HeretoHelp British Columbia
- **cultural awareness**: an attitude that includes awareness about differences between cultures
- **cultural sensitivity**: an attitude that recognizes the differences between cultures and that these differences are important to acknowledge in health care
- **cultural competency**: an approach that focuses on practitioners' attaining skills, knowledge, and attitudes to work in more effective and respectful ways with Indigenous patients and people of different cultures

Groups Facing Systemic Barriers, Discrimination, and Structural Violence

- certain groups are at greater risk for poorer health outcomes not due to their identity, but rather due to systemic barriers, discrimination, and structural violence (e.g. harmful policies, historic, and contemporary factors). The readers are strongly cautioned against pathologizing entire groups and are encouraged to further read into the historical factors that have contributed to creating systemic barriers which perpetuate inequities
- see *Colonization and Healthcare, PH7*; Ethical, Legal, and Organizational Medicine, *Indigenous Disproportionate Over-Representation of Biological, Psychological and Social Co-Morbidities, ELOM29; Indigenous Health, ELOM25*

Medical Officer of Health (MOH) (Ontario)
May be called "Medical Health Officer" (MHO) in other provinces
Appointed to each public health unit by the board of health
Position held by a Public Health and Preventive Medicine specialist physician
Responsibilities include oversight of a multidisciplinary team who:
- Collect and analyze epidemiological data
- Provide occupational and environmental health surveillance
- Implement health programs, including tobacco use prevention inspections (restaurants, physician's offices, tattoo parlors) and prenatal courses

The MOH, by law, can require an individual/premise/agency to take or refrain from any action due to a public health hazard (Section 13 and 22 of the Health Protection and Promotion Act)

Determinants of Health
Income and social status
Employment and working conditions
Education and literacy
Childhood experiences
Physical environments
Social supports and coping skills
Healthy behaviours
Access to health services
Biology and genetic endowment
Gender
Culture
Exposure to colonization and racialized prejudice
Racism
Source: Social determinants of health and health inequalities [Internet]. Government of Canada; [modified 2022 June 14; cited June 2022]. Available from https://www.canada.ca/en/public-health/services/health-promotion/population-health/what-determines-health.html

Ottawa Charter for Health Promotion (1986)
- Health promotion: the process of enabling people to increase control over, and improve their health
- Some health promotion can be achieved through clinical interactions with patients, but most health promotion is done at the population level by public health professionals and agencies through engaging stakeholders, formulating policy, and influencing upstream factors
- The Ottawa Charter is a framework for thinking about health promotion
- The Ottawa Charter states that governments and health care providers should be involved in a health promotion process that includes:
  1. Building healthy public policy
  2. Creating supportive environments
  3. Strengthening community action
  4. Developing personal skills
  5. Re-orienting health services

Table 2. Equity-Seeking Groups Facing Systemic Barriers

	Definition	Physical	Environmental	Personal Risk Factors	Population-Specific Interventions
Indigenous Peoples	Three distinct groups: First Nations (status and non-status Indians as per the Indian Act), Métis, and Inuit The original inhabitants of the land now called Canada All Indigenous communities and individuals experience the effects of colonization, but sometimes in very different ways	A history of surviving colonization and genocide Systemic racism Lower income Higher risk of experiencing violence and unemployment Homelessness	Limited overcrowded housing in disrepair in community Homelessness off-reserve Exposures to environmental toxins (poor drinking water) due to land dispossession and loss of environmental stewardship	Lifestyle adaptation, loss of traditional livelihood, unemployment, and lack of facilities Obesity (higher BMI) secondary to poorer access to high quality nutrition (food insecurity) Higher rates of smoking, substance misuse, and suicide secondary to intergenerational trauma	Movements towards decolonization and addressing the recommendations of the Truth and Reconciliation Commission Mental health awareness and increasing health literacy Indigenous-specific chronic disease management, including DM Culturally appropriate and interdisciplinary harm reduction, substance use treatment, and smoking cessation programs Cultural continuity (language and cultural programs are protective against depression and suicide) Incorporation of Traditional Medicine into the care plan (wellness journey) for Indigenous patients who want this to be part of their care Health practitioner training in cultural humility and safety
Black Individuals and Communities	Sub-Saharan African Ancestry, diverse cultures and histories (people may self-identify by geographic or ancestral regions (e.g. Caribbean, Ghanaian, Somali, African American, Black Canadian, etc.) but socially classified by society based on hair/skin phenotype as 'Black') 3rd largest "visible minority" group in Canada 43% Canadian-born	Variable, depending on socioeconomic status and immigrant status/history in Canada The Nova Scotian Black population has been in Canada for centuries; historically displaced into rural settings Newer immigrants tend to live in urban centres	Anti-Black systemic racism in Canada (officially acknowledged by the United Nations, the Canadian Public Health Association, and several provincial and local governments) has led to physical and mental health inequities High BMI Higher risk DM and HTN (poor data quality for identifying disparities in Canada due to lack of collection of race-based data)	Higher risk DM and HTN (poor data quality for identifying disparities in Canada due to lack of collection of race-based data)	Culturally-specific and safe practices Anti-racist approaches to care, policy, and programming Movements to reallocate police funding to more appropriate social services to curb police violence through transparency and public oversight
Isolated Seniors	Individuals >65 years of age	Elder abuse Lack of emotional support Isolation	Low hazard tolerance Higher rates of institutionalization Mobility issues	Inactivity Polypharmacy Medical comorbidities	Aging in place of choice Falls and injury prevention Mental health promotion Preventing abuse and neglect
Individuals/Children in Poverty	Based on LICOs LICO is an income threshold below which a family will likely devote a larger share of its income on the necessities of food, shelter, and clothing than the average family	Low income Family dysfunction Lack of educational opportunities	Housing availability Unsafe housing Lack of recreational space	Poor supervision Food insecurity High-risk behaviours	Improvements in family income most significant Access to early childhood education Access to safe housing
People with Disabilities	Includes impairments, activity limitations, and participation restrictions	Low income Low education status Discrimination Stigma	Institutionalization Barriers to access Transportation challenges	Substance misuse Poor nutrition Inactivity Dependency for ADLs	Transportation support Multidisciplinary care Unique support for individuals with specific disabilities (e.g. Trisomy 21)
New Immigrants	Person born outside of Canada who has been granted the right to live in Canada permanently by immigration authorities	Access to community services Cultural perspectives (including reliance on alternative health practices) Unstable or precarious housing	Exposure to diseases and conditions in country of origin, in current country of residence, or during immigration process (e.g. smoke from wood fires, incidence of TB)	Barriers finding employment that matches skills and qualifications Exposure to cultural discrimination and isolation which can impact health English language learner Healthy immigrant effect (health worsens over time to match that of the general population) Cultural or religious expectations	Women's health Mental health Comprehensive medical exam Dental and vision screening Vaccinations Cancer screening Receive language and employment training Support integrating into local community Benefit from culturally appropriate and culturally safe interventions, ideally developed in collaboration with the specific target communities
Persons Experiencing Homelessness	An individual who lacks permanent housing or adequate housing	Low income Food insecurity Mental illness	A history of colonial subjugation and land expropriation Exposure to temperature extremes Exposure to communicable diseases in shelters	Higher rates of adverse childhood events and subsequent substance use Greater risk of experiencing violence due to lack of housing and protection	Housing First policies Safe housing Addictions support Mental health

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population.
Sources: Shah, CP. The Health of Vulnerable Groups. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003.

Table 2. Equity-Seeking Groups Facing Systemic Barriers

	Definition	Physical	Environmental	Personal Risk Factors	Population-Specific Interventions
Refugees	Forced to flee country of origin because of a well-founded fear of persecution and given protection by the Government of Canada Refugee claimant: arrive in Canada and ask to be considered refugee	Post-traumatic stress disorders Depression Adjustment problems Partial health coverage via Interim Federal Health Program	Diseases and conditions in country of origin (e.g. malaria, TB, onchocerciasis, etc.) Direct and indirect effects of war	Employment English language learner Longstanding prior lack of access to health care (chronically neglected problems) Cultural or religious expectations	Vaccinations Women's health Mental health Comprehensive medical exam Dental and vision screening Political advocacy Language training Support for transitioning into the workplace Support integrating into local community
Religious Minorities	Religious minorities are those who do not practice the statistically dominant faith It varies by country, but in Canada, religious minorities are currently those who are not affiliated with one of the major Christian denominations Not all members of a minority faith practice and degree of identification varies per individual	Reduced employment options in Quebec due to laws banning government workers such as teachers, police officers, publicly employed lawyers, and court workers from wearing religious symbols like hijabs, turbans, and kippahs	At risk of experiencing hate crimes, especially those who wear visible religious symbols, such as Muslim women, Sikh men, and Jewish men	Poorer mental health Suboptimal health and care-seeking behaviours	If possible and when requested, offer patients a healthcare provider of the same gender Provide accessible multi-faith spaces and chaplain services in the hospital Instill a culture of inclusion beyond tolerance and provide religious accommodation where possible Proactively consult healthcare workers if they require alternative scheduling for religious holidays or fasting Collaborate with religious leaders and chaplains in supporting the health of their respective communities
LGBTIQ2S Individuals	Those who identify as lesbian (a homosexual woman), gay (a homosexual person irrespective of gender), bisexual (a person who is attracted to both genders), trans (a person whose core gender identity and/or gender expression does not align with the sex-assigned gender at birth; the sexuality of trans persons is independent of their gender diversity), intersex (an umbrella term to describe bodies that fall outside the strict male/female binary), questioning (regarding one's sexual or gender identity), queer (a historically reclaimed pejorative that is an umbrella term to encompass all sexual and gender diversities), two-spirited (a pan-indigenous term acknowledging gender diversity in uniquely traditional roles as distinct from western gender diverse identities), and asexual (a person who does not experience sexual attraction to others as distinct from celibacy; asexual individuals may still have sex)	Family violence Lower income Identity documents lacking correct name or sex designations Victims of hate crimes motivated by sexual orientation and/or gender identity; higher prevalence of hate crimes against racialized communities with greater fatality	Over-representation in youth homeless population Violence, harassment, and discrimination when seeking stable housing, employment, health, or social services	Higher rates of depression, anxiety, obsessive-compulsive and phobic disorders, suicidality, and self-harm Increased risk of alcohol, tobacco, and other substance misuse Double the risk for post-traumatic stress disorder than heterosexual people Greater participation in high-risk sexual practices related to HIV infection Deterioration of mental health due to multiple factors (internalized queerphobia, limited sociomedical infrastructure perpetuating/instigating underlying comorbidities)	Apply an intersectional lens to understand LGBTIQ2S populations (racialized, gender-diverse, traditional/cultural roles as in 2S) Gender-neutral language and the avoidance of heteronormative assumptions to invite patients to self-identify as gender or sexual minorities Increased awareness of the broader social, legal, and medical context in which LGBTIQ2S individuals live Improve recognition that individuals who belong to multiple marginalized communities may face additional barriers to maintaining good health
People who are/have been incarcerated	Individuals who are or have been incarcerated at a provincial correctional facility (sentences <2 years) or a federal correctional facility (sentences >2 years)	Inadequate access to physical and mental healthcare resources Limited social programming Higher rates of delayed or missed diagnoses Higher burdens of mental illness, substance use disorders, and chronic illness Stigma following release from prison, limiting full social reintegration and increasing likelihood of re-offense	Social isolation and segregation Increased stress from risk of violence	Racialized individuals (including those who are Black, Indigenous, and other people of colour) experience disproportionate police attention and higher rates of criminalization Past involvement with the criminal justice system or over-criminalization of certain activities (e.g. sex work) Personal history of homelessness or low socioeconomic status	Address stigma towards people with a history of incarceration Increase availability and funding to healthcare in correctional facilities Improve re-integration services to reduce recidivism Invest in community services, including mental health services, housing initiatives, and social workers

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population.
Sources: Shah, CP. The Health of Vulnerable Groups. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003.

Screening for Poverty
- poverty is not always apparent despite being widespread (20% of families in Ontario live in poverty)
- poverty is a risk factor for many chronic diseases, cancer, and mental illness
- women, Indigenous peoples, new immigrants, and LGBTQ+ are some of the groups at highest risk of living in poverty
- as a healthcare provider, addressing systemic barriers and the SDOH is dynamic and complex
- primary healthcare providers can screen for poverty by asking the following two questions:
  - step 1: "Do you ever have difficulty making ends meet at the end of the month?"
    - for living below the poverty line, sensitivity 98% and specificity 40%
  - step 2: "Have you filled out and sent in your tax forms?"
    - tax returns are required for accessing many income security benefits like GST/HST credit, working income tax benefits, property tax credits, child benefits, etc.
    - connect your patients to social and financial supports (e.g. ODSP, Ontario Works) and resources (e.g. a free community tax clinic) accordingly

Indigenous Health in Canada

Definitions
- Indigenous peoples represent approximately 4.9% of the total population of Canada in 2016 and speak over 70 Indigenous languages
- 3 distinct groups of Indigenous peoples in Canada (per sec. 35 of the Constitution Act 1982): First Nations (status and non-status), Métis, and Inuit
  - First Nations: includes over 600 diverse communities in Canada; status vs. non-status refers to the registration of First Nations peoples under the Indian Act (1876), which, in addition to the establishment of the Department of Indian Affairs, was originally established by the government to administer/manage Treaty commitments, and to remove self-governing and traditional practice rights. The Indian Act impacts the lives of countless Indigenous peoples, families, and communities from birth to death
  - Métis: descendants of the First Nations and European settlers; nearly 2/3 residing in cities, greatest proportion in Ontario and the prairie provinces
  - Inuit: roughly 75% of this population of 70000 resides in the 4 Canadian Regions known as Inuit Nunangat, the Inuit Homeland. These include: Nunavut, Nunavik (Northern Quebec), Nunatsiavut (Labrador), and Inuvialuit (Northwest Territories). The majority of Inuit live in Nunavut (30135), followed by Nunavik (11800), Inuvialuit (3110), and Nunatsiavut (2285). Another 17690 Inuit live outside of Inuit Nunangat, many in urban centres in southern Canada, including Ottawa, Edmonton, and Montréal

Young and Growing Populations
- between 2006-2016 the Indigenous populations have increased by 42.5%, 4 times that of non-Indigenous Canadian population growth
- 32.1 is the average age of the Indigenous population, about 8 years younger than the non-Indigenous Canadian population
- the aging Indigenous population is also growing, with anticipated doubling of >65 years age group by 2036

Colonization and Healthcare
Colonizers have perpetrated specific acts throughout Canadian history that have greatly impacted the physical, mental, emotional, and spiritual health of Indigenous peoples. Physicians should therefore be aware of the historical (and current) underpinnings of Indigenous health disparities, and the way in which health care professionals, including physicians, have acted as agents of the colonial agenda historically, which are discussed here, and their responsibility to redress previously damaged healthcare relationships (see Ethical, Legal, and Organizational Medicine, *Resources in Indigenous Health*, ELOM30). Despite institutionalized abuse and assimilation, Indigenous people have survived remarkable injustice and have built resilience through traditional knowledge and practices.

Residential Schools (1870s-1996)
The residential school era is well-known for its lasting and damaging effects on many generations of Indigenous people. Many Indigenous students suffered from poor nutrition, hygiene, and living conditions, as well as physical, sexual, and psychological abuse from teachers and others in power. The intent of residential schools to assimilate Indigenous people also led to spiritual harms through significant loss of traditional language and culture. Residential school survivors report poorer general and self-rated health as well as increased rates of chronic and infectious diseases, mental distress, depression, substance use, and suicide. Importantly, many of these outcomes extend to subsequent generations (i.e. intergenerational trauma).

The term "residential school syndrome" has been proposed to better characterize the traditional DSM-V definition of post-traumatic stress disorder with additional criteria specific to residential school survivors, such as tendency to misuse alcohol and drugs (often at a young age), loss of cultural knowledge, violent or angry outbursts, and difficulty parenting. Treatment approaches must take into account a holistic view of all these criteria, rather than simply focusing on one aspect, like substance use, which often perpetuates negative stereotypes.

New Immigrants to Canada

Mandatory medical exams on entry to Canada by a designated medical practitioner

Complete medical examination for persons of all ages

Chest x-ray and report for persons ≥11 yr

Urinalysis for persons ≥5 yr

Syphilis serology for persons ≥15 yr

HIV testing for applicants ≥15 yr, as well as for those children who have received blood or blood products, have a known HIV-positive mother, or have an identified risk. An ELISA HIV screening test should be done for HIV 1 and HIV 2

Serum creatinine for persons ≥15 yr, and children with a history of HTN (resting BP >150/90 mmHg), DM, kidney disease, or signs of impaired renal function

Provide compassionate psychosocial assessment, be aware of increased prevalence of mental health issues (e.g. PTSD, depression, intimate partner violence)

Assess immunization documents and develop catch-up schedule

Source: Citizenship and Immigration Canada Handbook
https://www.canada.ca/en/immigration-refugees-citizenship/corporate/publications-manuals.html

Traditional and Complementary Medicine Use Among Indigenous Cancer Patients in Australia, Canada, New Zealand, and the United States: A Systematic Review

Integr Cancer Ther 2018;17(3): 568-581

Purpose: To systematically review the use of traditional Indigenous and complementary medicines among Indigenous cancer patients in Australia, Canada, New Zealand, and the United States.

Methods: Studies on the use of traditional Indigenous and complementary medicines among Indigenous cancer patients in Australia, Canada, New Zealand, and the United States published between January 2000 and October 2017 were eligible for inclusion.

Results: 21 articles based on 18 studies were included. Traditional Indigenous and complementary medicines were used by between 19% to 57.7% of Indigenous patients. These modalities were most often used in combination with conventional cancer treatments to meet spiritual, emotional, and cultural needs. These treatments had multiple perceived spiritual, emotional, and cultural benefits. Traditional Indigenous and complementary medicine use was influenced by a patient's perceptions of their healthcare practitioner's attitudes towards these modalities.

In Canada, many Indigenous healing practices include drumming, singing, smudging, herbal teas, sweat lodges, and other ceremonies. Healthcare providers are encouraged to research and explore these options as an additional therapeutic tool for Indigenous patients requesting them. Not all Indigenous patients will request such treatments and so perhaps first ask patients, "What do I need to know about you as a person to give you the best care possible?"

The Truth and Reconciliation Commission (TRC) (2015) is a document jointly created by the Canadian government and residential school survivors that preserves in writing the truth of residential schools and delineates recommendations for reconciliation. Many TRC recommendations pertain directly to health and healthcare providers. Unfortunately, eight years later they remain recommendations and have not become Calls to Action.

Nutrition Trials

From 1942 to 1952, nutritional scientists in conjunction with the Canadian government performed unethical research on Indigenous people with the aim of "studying the state of nutrition of the Indian." The James Bay Survey is perhaps the most well-known of these studies conducted on the Attawapiskat and Rupert's House Cree First Nations, though many were conducted on residential school children as well. One of the lead physician-scientists was Dr. Frederick Tisdall (inventor of Pablum), former president of the Canadian Paediatric Society and pediatrician at the Hospital for Sick Children in Toronto, Ontario. Some unethical and arguably criminal acts committed by researchers were:

- lack of informed consent from parents or children
- Indigenous children were kept malnourished over a two-year period to establish a baseline
- one group of children received a flour mix not yet approved for sale that caused them to develop anemia, contributing to greater morbidity and possibly mortality in this group with no therapeutic intervention
- in an effort to control as many factors as possible, dental care was denied to observe the progression of dental cavities and gingivitis in the setting of malnutrition

Impact of Sustained Caloric Restriction on Residential School Survivors and Other Generations

- sustained caloric restriction can cause height stunting, induce physiological changes to prioritize fat over lean mass, and increased risk of developing type 2 diabetes
- stunting negatively impacts neurological, psychological, and immune systems
- due to sustained starvation, "the child's physiology is essentially 'programmed' by hunger to continue the cycle of worsening effects, with their bodies displaying a rapid tendency for fat-mass accumulation when nutritional resources become available"
- other generations are at risk of having a higher BMI and developing obesity

Tuberculosis, Tuberculosis Sanatoriums, and "Indian Hospitals"

European colonizers brought tuberculosis (TB) to Indigenous populations as early as the 1700s. Indigenous communities, particularly the Inuit, already had risk factors predisposing the spread of TB. For example, there was malnutrition from food scarcity and overcrowding on federally mandated reserves after forced relocation from traditional territories. From 1930-1940, death rates from TB in Inuit populations were roughly 700 per 100000, among the highest ever recorded in a human population. For comparison, TB was the tenth leading cause of death globally in 2016 at a crude death rate of 17 per 100000, while ischemic heart disease was the first at 126 per 100000. This led the Canadian government to forcibly relocate many Indigenous people to TB sanatoriums and "Indian hospitals," often hundreds of kilometres away. The average length of stay at these institutions was 2.5 years and many patients never returned home.

The TB health crisis persists today; in 2016, the average annual incidence rate of TB among the Inuit in Canada was roughly 296 times higher than Canadian-born non-Indigenous people. In March 2018, the national representational organization for Inuit people in Canada, called Inuit Tapiriit Kanatami (ITK), and the Government of Canada committed to reduce TB rates across Inuit communities by 50% by 2025 and to eliminate TB by 2030 in a project called the Inuit Tuberculosis Elimination Framework.

It is worth noting that "Indian hospitals" were initially welcomed by many First Nations who were under the impression that reasonable healthcare was part of treaty terms. In reality, "Indian hospitals" were crowded, underfunded, and poorly staffed, serving to segregate sick Indigenous people from the rest of the population. They were also the site of the cycle of apprehension, coercive sterilization, chemical and physical restraints, and scientific experimentation, all of which inflicted significant morbidity and mortality. When the Canadian government began closing these hospitals in the 1960s, Indigenous people continued to fight for their right to healthcare, which was finally recognized in the Indian Health Policy of 1979.

Coerced Sterilizations

Throughout the twentieth century, eugenics programs existed across the country. In the 1920s-1930s, both Alberta and British Columbia legalized eugenic policies in the Sexual Sterilization Acts which were not repealed until the 1970s. To limit reproduction of "unfit" people in the eyes of the government, Indigenous women were disproportionately targeted. This is referred to as forced or coerced sterilization and, according to various accounts by Indigenous women across the country, involved any number of the following:

- tubal ligations being performed without consent
- being falsely told that a procedure is reversible
- being pressured into signing consent forms while actively in labour or on operating tables
- being given an ultimatum to undergo a tubal ligation or risk child apprehension

It is important to note that many sterilizations also occurred outside legislation, in federally run "Indian hospitals," and some have been documented as recently as 2019. At least 100 Indigenous women have come forward with accounts of coerced sterilization by physicians and nurses, spanning from the 1970s until 2019.

Social Prescribing
Consider social prescribing: a holistic approach which involves the integration, referral to, and collaboration between social and medical services. Promotes health and wellbeing by connecting individuals to their community

A framework for building primary care capacity to address the social determinants of health
In Toronto, the St Michael's Hospital Academic Family Health Team developed the SDOH Committee to analyze how social factors affect patients and support the development and implementation of interventions. Informed by this work and existing literature, a conceptual framework was developed to demonstrate how primary care organizations can intervene in SDOH:

1. Collect data to identify "upstream" causes of downstream problems
2. Use the data to change the care provided to individuals and in practice management
3. Use your data to drive change at the organizational level
4. Use your data and experience to inform system evolution
5. Use your data and experience to create a foundation for "upstream" advocacy

Source: Pinto, A.D. and Bloch G. Framework for building primary care capacity to address the social determinants of health. Canadian Family Physician. 2017, 63 (11) e476-e482

Sixties Scoop and Indigenous Child Welfare

The "Sixties Scoop" (Johnson, 1983) (1951-1980s) refers to the government-mandated practice of removing Indigenous children from their families without consent for placement in foster care or adoption. As residential schools started to close, many children were transitioned to child welfare facilities as the state deemed Indigenous parents unfit to care for their children – a legacy that persists today. Similar to the Indian Residential School system, the goal was to assimilate Indigenous children into a non-Indigenous family, rather than to directly provide child welfare to Indigenous communities. Though Indigenous bands have increasingly been allowed to provide their own child welfare, Indigenous children are still overrepresented in foster care. In 2016, Indigenous youth ages 0 to 4 made up about half of all foster children in private households, despite being only 8% of total youth in this age group in Canada. Youth with a history in government care may be at greater risk for substance misuse, street involvement, and incarceration.

To this day, Indigenous children are disproportionately represented in the child welfare system and are often apprehended for reasons directly related to the routine conditions of poverty. The apprehensions that continue today echo the practices of the Sixties Scoop and residential school eras; the displacement of Indigenous children separates them from their language and culture and hinders the ability of Indigenous families to build resilience. Importantly, many Indigenous mothers and families avoid accessing healthcare services for fear of their children being apprehended.

Indigenous Approaches to Health and Wellness

- it is important to recognize the significant diversity amongst Indigenous nations in the land now known as Canada. Even within the same nation or language group, there will be variability in practices. Despite this diversity, there are some ideas that recur across many nations
- restoring balance in the four realms of spiritual, emotional, mental, and physical health of a person acting as an individual, as well as a member of a family, community, and nation
  - ideas represented by the medicine wheel of First Nations peoples, the Learning Blanket of Inuit peoples, and the Métis tree model all share a worldview based on holistic lifelong learning and wellness
  - Indigenous medicines may take many forms (song, dance, smudge, ceremonies, plant medicines, etc.)
  - practiced by experts who have decades of apprenticeship
  - while allopathic medicine often focuses on treating illness (like high blood pressure or diabetes), Indigenous medicine may understand the cause of a condition and the approach to healing in a different way than a biomedical guideline
  - Indigenous medicine may focus on quality of life and not just cure
  - cultural humility
    - cultural humility is a respectful, person-centered way of bringing curiosity and compassion when a patient is willing to come for support
    - it takes courage to be humble enough to admit that we do not know what we do not know
    - Indigenous medicine is thousands of years old and so far has generally eluded evaluation via randomized controlled trials
    - Traditional Medicine is unlikely to interfere with Western Therapies
    - Latin root of "curiosity" is "cura," which means "to care." Caring about someone's healing and their beliefs about what may help them heal is a powerful act of witnessing and honouring. Beginning with the belief that a person has wisdom about themselves that no one else does and that we can be supporters of their healing, if they consent, can be a way to honour the inherent wholeness of a person seeking care. This is especially true of Indigenous patients for whom regaining self-determination is tantamount to regaining their wellness.
  - before assuming that an Indigenous person is interested in using traditional medicine, it is important to begin with questions and curiosity. Dr. Chantal Perrot speaks about the Patient Dignity Questionnaire which advises healthcare workers to first ask patients, "What do I need to know about you as a person to give you the best care possible?"
  - National Indigenous Health Organization (NIHO) offers 8 guidelines on practicing culturally safe health care for Indigenous patients including the need to allow Indigenous patients to access ceremony, song, and prayer; the need for information and for family support; guidelines for the appropriate disposal of body parts and for handling death

Disease Prevention

Natural History of Disease

- course of a disease from onset to resolution
  1. pathological onset
  2. presymptomatic stage: from onset to first appearance of symptoms/signs
  3. clinical manifestation of disease: may regress spontaneously, be subject to remissions and relapses, or progress to death

Surveillance

- the continuous, systematic collection, analysis, and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice

Sources: Public health surveillance [Internet]. World Health Organization. Available from https://www.who.int/topics/public_health_surveillance/en/

Passive Prevention
Measures that operate without the person's active involvement (e.g. airbags in cars) are more effective than active prevention, which are measures that a person must do on their own (e.g. wearing a seatbelt)

Example of Primary Prevention
HPV 9-Valent Vaccine and Its Efficacy in the Prevention of Cervical Cancer

This is a nonavalent HPV vaccine covering strains 6, 11, 16, 18, 31, 33, 45, 52, and 58

The efficacy of this vaccine was studied in 4 randomized, double-blind, placebo-controlled trials on females between 11 and 26 yr and was found to prevent nearly 100% of precancerous cervical changes for up to 4 yr after vaccination

- types of surveillance
  - **passive surveillance**: reporting of disease data by all institutions that see patients, relying solely on the cooperation of healthcare providers (laboratories, hospitals, health facilities, and private practitioners)
    - most common, least expensive, but difficult to ensure completeness and timeliness of data
  - **active surveillance**: regular visits to health facilities for reviewing medical records to identify suspected cases of disease under surveillance, or active testing of a population for the presence of a disease
    - resource-intensive, used when a disease is targeted for eradication where every possible case must be investigated, or for outbreak investigations
  - **sentinel surveillance**: selective reporting of disease data from a limited network of carefully selected reporting sites with a high probability of seeing cases in question
    - well-designed system can be used to signal trends, identify outbreaks, and monitor the burden of disease in a community in a timely and cost-effective manner compared to other kinds of surveillance
    - may not be as effective in identifying rare diseases, or diseases that occur outside the catchment area of sentinel sites

Sources: World Health Organization. Public Health Surveillance. Accessed from:
https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/en/
https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/en/
https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/sentinel/en/

Disease Prevention Strategies

- measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

Table 3. Levels of Disease Prevention

Level of Prevention	Goal	Examples
Primordial	Preventing the development of risk factors	Education that begins in childhood about behaviour that can harm health Programs that encourage physical activity
Primary	Protect health and prevent disease onset Reducing exposure to risk factors	Immunization programs (e.g. measles, diphtheria, pertussis, tetanus, polio, see Pediatrics, P5) Smoking cessation Seatbelt use See *Landmark Public Health and Preventive Medicine Trials, PH33* for more information on VAXICOL, which details the impact of influenza vaccination of nursing home staff on mortality of residents
Secondary	Early detection of (subclinical) disease to minimize morbidity and mortality	Mammography Routine Pap smears FIT (vs.FOBT vs. colonoscopy)
Tertiary	Treatment and rehabilitation of disease to prevent progression, permanent disability, and future disease	DM monitoring with HbA1c, eye exams, foot exams Medication to manage chronic conditions

Source: Basic Concepts in Prevention, Surveillance, and Health Promotion. AFMC Primer on Population Health. http://phprimer.afmc.ca/Part1-TheoryThinkingAboutHealth Chapter4BasicConceptsInPreventionSurveillanceAndHealthPromotion/Thestagesofprevention

Screening (Secondary Prevention)

- "screening is a strategy used in a population to identify the possible presence of an as-yet-undiagnosed disease in individuals without signs or symptoms"
  - screening vs. case finding: screening tests are not diagnostic tests
  - the primary purpose of screening tests is to detect early disease or risk factors for disease in large numbers of apparently healthy individuals. The purpose of a diagnostic test is to establish the presence (or absence) of disease as a basis for treatment decisions in symptomatic or screen positive individuals (confirmatory test). Both screening and case finding seek to risk stratify for further investigation
  - to minimize biases and harms, and maximize benefits, screening is best done at the population level, not the individual clinical level, as part of a screening program (e.g. provincial breast cancer screening program vs. screening by primary care/family physicians)
- **types of screening**
  - **universal screening**: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
  - **selective screening**: screening of targeted subgroups of the population at risk for a disease (e.g. mammography in women >50 yr)
  - **multiphasic screening**: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)
- **types of bias in screening**
  - **lead-time bias**: overestimation of survival time 'from diagnosis' when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening
  - **length-time bias**: overestimation of the survival time due to screening at one time point including more stable cases than aggressive cases of disease, which may have shorter survival times

Does Evidence Support Supervised Injection Sites?
Can Fam Physician 2017;63(11):866
- Clinical question: Do supervised injection sites (SISs) reduce mortality, hospitalizations, ambulance calls, or disease transmission?
- Bottom line: The best evidence from cohort and modelling studies suggests that SISs are associated with lower overdose mortality (88 fewer overdose deaths per 100000 person-years (PYs)), 67% fewer ambulance calls for treating overdoses, and a decrease in HIV infections. Effects on hospitalizations are unknown

Smoking Cessation: Vaping Compared with Traditional Nicotine Replacement Therapies: a Systematic Review and Meta-analysis
BMJ Open 2021;11:e044222
Pooled results from six randomized controlled trials identified no difference in smoking cessation, the proportion of participants reducing smoking consumption, mean reduction in cigarettes smoked per day, or harms, between e-cigarettes and traditional nicotine replacement therapy. Most studies were judged to have a high risk of bias, resulting in the overall quality of evidence as low. More research is necessary prior to establishing recommendations related to e-cigarettes as smoking cessation tools.

Traditional and Complementary Medicine Use Among Indigenous Cancer Patients in Australia, Canada, New Zealand, and the United States: A Systematic Review
Integr Cancer Ther 2018;17(3): 568-581
Purpose: To systematically review the use of traditional Indigenous and complementary medicines (T&CM) among Indigenous cancer patients.
Methods: Studies on the use of T&CM among Indigenous cancer patients in Australia, Canada, New Zealand, and the United States published between January 2000 and October 2017 were eligible for inclusion.
Results: Twenty-one articles based on 18 studies were included. T&CM were used by between 19% to 57.7% of Indigenous patients. These modalities were most often used in combination with conventional cancer treatments to meet spiritual, emotional, and cultural needs. These treatments had multiple perceived spiritual, emotional, and cultural benefits.
Conclusions: These findings demonstrate an important role for T&CM in Indigenous cancer patients in these countries. Importantly, T&CM use was influenced by a patient's perceptions of their healthcare practitioner's attitudes towards these modalities.

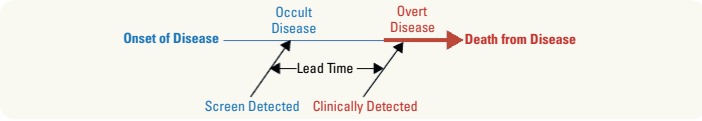


Figure 2. Lead-time bias

Table 4. Ideal Criteria for Screening Tests

Disease	Test	Health Care System
Causes significant suffering and/or death Natural history must be understood Must have an asymptomatic stage that can be detected by a test Early detection and intervention must result in improved outcomes	High sensitivity Safe, rapid, easy, relatively inexpensive Acceptable to providers and the population Continuously utilized	Adequate capacity for reporting, follow-up, and treatment of positive screens Cost effective Sustainable program Clear policy guidelines on who to treat

Adapted from: Shah CP. Public Health and Preventive Medicine in Canada, 5th ed. Toronto: Elsevier, 2003

Health Promotion Strategies

- health promotion refers to the process of enabling individuals and communities to increase control over, and improve, their health and well-being through a range of social and environmental interventions
- per the WHO's 1986 Ottawa Charter for Health Promotion, there are five key strategies: building healthy public policies, creating supportive environments, strengthening community action, developing personal skills, and reorienting health services

Table 5. Disease Prevention vs. Health Promotion Approach

Disease Prevention	Health Promotion
Health = absence of disease	Health = positive and multidimensional concept
Medical model (passive role)	Participatory model of health
Aimed mainly at high-risk groups in the population	Aimed at the population in its total environment
One-shot strategy aimed at a specific pathology	Diverse and complementary strategies aimed at a network of issues/determinants
Directive and persuasive strategies enforced in target groups	Facilitating and enabling approaches by incentives offered to the population
Focused mostly on individuals	Focused on a person's health status and environment
Led by professional groups from health disciplines	Led by non-professional organizations, civic groups, local, municipal, regional, and national governments

Source: Shah CP. Public Health and Preventive Medicine in Canada, 5th ed. Toronto: Elsevier, 2003

Healthy Public Policy

- purpose: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- governments and non-governmental agencies need to consider the cost and acceptability of proposed public health interventions (e.g. more invasive or costly measures should be justified by the extent of beneficial impacts on people's lives)
- the Nuffield Intervention Ladder provides one way of ranking the level of intrusion and hence a need for proportionate benefit of health promotion interventions at a population level
- methods
  - **fiscal**: imposing additional costs (e.g. taxes on tobacco and alcohol)
  - **legislative**: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  - **social**: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)

Behaviour Change

- behaviour is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community
- health education serves to: increase knowledge and skills and promote healthy behaviours

Health Belief Model (1975)

- a psychological model that explains and predicts individual short- and long-term health behaviours based on one's beliefs and attitudes
- based on the assumption that one will adopt a beneficial health behaviour if the following three beliefs are present:
  - the negative health outcome is avoidable
  - expects that the health outcome can be prevented if the recommended health behaviour is adopted
  - the individual can be successful in adopting the health behaviour
- six concepts:
  - four concepts influencing one's "readiness to act" – perceived susceptibility, perceived severity, perceived benefits, perceived barriers
  - cues to action: stimuli that can trigger health action
  - self-efficacy: confidence in one's ability to take a health action

A Snapshot of the Opioid Crisis in Canada

Canada is experiencing a crisis of opioid-related overdose and death. Between January 2016 and September 2019, there were more than 14700 deaths in Canada related to opioids. There were also 19490 hospitalizations and 17000 emergency services. Individuals 25-34 y/o are at the greatest risk of overdose death (1 in 6 deaths), but rates have increased for all adult ages. Deaths are most commonly unintentional. Heroin, fentanyl, and hydromorphone are most commonly involved. The highest rates of opioid-related overdose and death are found in British Columbia. An estimated 300 per million British Columbians died in relation to opioid use in 2017. More died from opioids than homicide, motor vehicle accidents, and suicide combined. In 2017, deaths from opioids in Ontario were ~1250, while deaths from motor vehicle accidents were ~450. Fentanyl or a fentanyl analogue were involved in more than 70% of cases, increased from 55% in 2016.

Sources: J Addict Med. Measuring the Burden of Opioid-related Mortality in Ontario, Canada . Latest Trends in Opioid-Related Deaths in Ontario: 1991 to 2015, Toronto: Ontario Drug Policy Research Network. Health Canada. March 2018. Opioid-related harms in Canada. Health Canada. March 2020

See Landmark Public Health and Preventive Medicine Trials table for more information on the Swedish Two-County Trial, which details the long-term effect of mammographic screening on breast cancer mortality

Transtheoretical Model Stages of Change for Dietary and Physical Exercise Modification in Weight Loss Management for Overweight and Obese Adults

Cochrane DB Syst Rev 2014:CD008066

Purpose: To explore the efficacy of dietary and physical activity interventions based in the transtheoretical model of change for sustained weight loss after one yr in overweight or obese adults.

Methods: RCTs comparing the use of weight loss or physical activity intervention grounded in the transtheoretical model of change to usual care for weight loss in adults who were overweight or obese were eligible for inclusion. Interventions had to be carried out by healthcare professionals or trained lay people. Weight loss or change in BMI was required as an outcome measure.

Results: Three studies including a total of 2971 participants were included in this review. Interventions grounded in this model did have positive effects on physical activity and dietary habits that included increased exercise duration and frequency, reduced fat intake, and increased fruit and vegetable consumption. The evidence for sustained weight loss at one yr was inconclusive (mean difference in favour of the transtheoretical model was between 2.1 kg and 0.2 kg at 24 mo).

Stages of Change Model

- provides a framework in which the Health Belief Model is applied to facilitating behaviour change (e.g. quitting smoking)

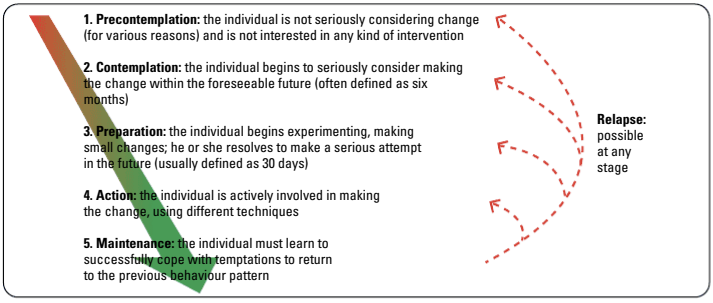

1. Precontemplation: the individual is not seriously considering change (for various reasons) and is not interested in any kind of intervention
2. Contemplation: the individual begins to seriously consider making the change within the foreseeable future (often defined as six months)
3. Preparation: the individual begins experimenting, making small changes; he or she resolves to make a serious attempt in the future (usually defined as 30 days)
4. Action: the individual is actively involved in making the change, using different techniques
5. Maintenance: the individual must learn to successfully cope with temptations to return to the previous behaviour pattern
Relapse: possible at any stage

Figure 3. Stages of change model
Source: Prochaska JO, DiClemente CC, and Norcross JC. In search of how people change. Applications to Addictive Behaviours. Am Psychol 1992;47:1102-1114

Risk Reduction Strategies

- **risk reduction**: lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
- **harm reduction**: a set of strategies aimed to reduce the negative consequences of drug use and other risky behaviours (e.g. needle exchange programs)

Source: Shah, CP. Concepts, Determinants, and Promotion of Health. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003

Community Needs Assessment

- a community needs assessment studies a community's health gaps and pairs identification of that community's existing resources and strengths to find solutions to address those gaps. This assessment strongly values interviewing community members to gather their concerns and proposed solutions. Steps include:
  1. define the community and understand its history and demographic characteristics to formulate context for subsequent data collection
  2. understand what matters to community stakeholders (e.g. interviews, surveys, focus groups)
  3. use evidence (e.g. mortality rate, feasibility), prioritize each concern
  4. identify barriers that may prevent a concern from being addressed and propose solutions using community-based resources

Measurements of Health and Disease in a Population

MEASURES OF DISEASE OCCURRENCE

Rates, Ratios, and Proportions

- a rate measures the frequency of an event in a defined population over a specific period of time (e.g. number of opioid overdoses in Canada in one year)
- a ratio compares the magnitude of one quantity to another (e.g. ratio of women to men with lupus)
- a proportion is a ratio where the numerator is a part of the denominator (e.g. proportion of deliveries complicated by placental abruption)

Incidence Rate

- number of new cases in a population over a specific period of time

Prevalence

- total number of cases in a population over a defined period of time
- two forms of prevalence
  - **point prevalence**: assessed at one point in time
  - **period prevalence**: assessed over a period of time, therefore including new cases and excluding cases that terminate (cure or death)
- a function of the incidence rate and disease duration from onset to termination
- favours the inclusion of chronic over acute cases and may underestimate disease burden if those with short disease duration are missed
- prevalence estimates are useful for measuring disease burden and therefore help in the planning of facilities and services

Principles of Standardization

- When comparing a health measure (e.g. mortality) between two populations (or the same population at different time points) that differ in characteristics known to influence that outcome (e.g. age), standardization is used to control for the effect of that factor
- Standardization is either direct or indirect
- Indirect standardization is expressed as standardized outcome ratio. For example, Standardized Mortality Ratio (SMR) is calculated using age specific rates for a reference population, as well as age structure and total cases for a sample/known population. (e.g. an SMR of 100 signifies that deaths are at the expected level, a SMR of 110 indicates a death rate 10% higher than expected)
- Direct standardization is expressed as a rate (i.e. using age specific rates in a known/sample population against a standard population)

Smoking Cessation: Vaping Compared with Traditional Nicotine Replacement Therapies: A Systematic Review and Meta-analysis
BMJ Open 2021;11:e044222
Purpose: To compare the effects of electronic nicotine device systems (ENDS) compared to other types of nicotine replacement therapies (NRT) as smoking cessation tools.
Methods: Systematic review and meta-analysis of randomized control trials comparing ENDS to NRT for smoking cessation.
Results: No difference was detected in smoking cessation rates (rate ratio (RR) 1.42; 95% CI, 0.97-2.09), proportion of those who reduced smoking (RR 1.25; 95% CI, 0.79-1.98) or harms (RR 0.96; 95% CI, 0.76-1.20) between ENDS and NRT groups. However, the quality of evidence was low to very low with a high risk of bias.
Conclusion: Although no difference was detected between ENDS and NRT as smoking cessation tools, the quality of evidence was low and therefore more research is necessary prior to establishing recommendations related to ENDS as smoking cessation tools.

Age-Standardized Rate
- adjustment of the crude rate of a health-related event using a "standard" population
- standard population is one with a known number of persons in each age and sex group
- standardization prevents bias that can occur when crude rates from two dissimilar populations are compared (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time)
- this allows for the calculation of a Standardized Mortality Ratio (SMR), where SMR = (observed number of deaths)/(expected number of deaths)

MEASURES OF MORTALITY

Life Expectancy
- the expected number of years to be lived by a newborn based on age-specific mortality rates at a selected time

Crude Death Rate
- mortality from all causes of death per 1000 in the population

Infant Mortality Rate (IMR)
- number of reported deaths among children <1 yr of age during a given time period divided by the number of reported live births during the same time period and expressed as per 1000 live births per year

Maternal Mortality Rate (MMR)
- "number of deaths of women during pregnancy and due to puerperal causes […] per 1000 live births in the same year"

MEASURES OF DISEASE BURDEN

Potential Years of Life Lost (PYLL)
- calculated for a population using the difference between the actual age at death and a standard/expected age at death
- increased weighting of mortality at a younger age

Disability Adjusted Life Year (DALY)
- number of years lost due to premature mortality + number of years lost due to disability, where 0 = a year of perfect health and 1 = death
- both premature death and time spent with disability accounted for; these disabilities can be physical or mental
- used to assess burden of diseases in a population

Quality Adjusted Life Year (QALY)
- years of life weighted by quality (utility is a proxy for quality), ranging from 0 (= death) to 1 (= perfect health). Weights are assigned based on large studies that assessed the effect of various conditions on quality of life (e.g. blindness = 0.3)
- it is possible to have "states worse than death" (e.g. QALY <0 for extremely serious conditions)
- usually used as an economic measure to assess the value for money of medical interventions

Top 10 Causes of DALYs in Canada, 2019
1. Neoplasms
2. Cardiovascular diseases
3. Musculoskeletal disorders
4. Neurological disorders
5. Mental disorders
6. Other non-communicable diseases
7. Unintentional injuries
8. Chronic respiratory diseases
9. Diabetes and kidney diseases
10. Substance use disorders

Source: Global Burden of Disease Compare | Viz Hub [Internet]. Seattle (WA): University of Washington, Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2021 Mar 28]. Available from: https://vizhub.healthdata.org/gbd-compare/

For additional rate calculations see *Steps to Control an Outbreak, PH24*

Consult the Public Health Agency of Canada for examples and latest statistics

Government of Canada: Chapter 3: The chief public health officer's report on the state of public health in Canada 2008 - our health [Internet]. Our population, our health, and the distributions of our health; [updated 2008 Jun 6]. Available from: https://www.canada.ca/en/public-health/corporate/publications/chief-public-health-officer-reports-state-public-health-canada/report-on-state-public-health-canada-2008/chapter-3b.html

Sources: Shah, CP. Health indicators and data sources. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003

The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC primer on population health [Internet]. Methods: measuring health; [cited 2006 Mar 25]. Available from https://phprimer.afmc.ca/en/

Epidemiology

Population
- a defined collection of individuals/regions/institutions/etc. (e.g. individuals defined by geographic region, sex, age)

Sample
- a selection of individuals from a population
- types
  - random: all members are equally likely to be selected
  - systematic: an algorithm is used to select a subset
  - stratified: population is divided into subgroups that are each sampled
  - cluster: grouped in space/time to reduce costs
  - convenience: non-random inclusion, for populations that are difficult to reach (e.g. people with precarious living conditions)

SPIN: use a **SP**ecific test to rule **IN** a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive
SNOUT: use a **SEN**sitive test to rule **OUT** a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative

Sample Size
- increasing the sample size increases the statistical precision of the observed estimate, resulting in more narrow confidence intervals
- increasing the sample size decreases the probability of type I and type II errors
- increasing sample size does not alter the risk of bias/confounding

Bias
- systematic error leading to an incorrect estimate of the true association between exposure and outcome
- can occur at several points in study execution (e.g. collection, analysis, interpretation, publication, or review of data)
- **selection bias**: a systematic error in the recruitment or retention of study participants
- **Berkson's bias** occurs in a case-control study using hospitalized controls, as they may not be a representative sample of the population due to the complexity that led to their hospital admission
- **non-response bias** occurs when participants differ from non-participants in a study, in that those who volunteer may be healthier
- **loss to follow-up bias** occurs when dropout rates differ between study groups and patients who dropped out are different from those who did not
- **information bias**: the way in which information is collected about study participants is inadequate
- **recall bias** occurs when individuals with disease may be more likely to incorrectly recall/believe they were exposed to a possible risk factor than those who are free of disease
- **interviewer bias** occurs when interviewers are unblinded to outcome status and this knowledge biases their behaviour
- **observer bias** occurs when knowledge of exposure status (e.g. race, gender) biases the observer towards a diagnosis; this occurs more commonly with subjective diagnoses like those found in psychiatry

Confounder
- a variable that is related to both the exposure and outcome but is not a mediator/in the exposure-outcome relationship
- distorts the estimated effect of an exposure if not accounted for in the study design/analysis (e.g. late maternal age could be a confounder in an investigation of birth order >4 and risk of developing Trisomy 21)
- randomization, stratification, matching, and regression modelling can help minimize confounding effects, usually not be eliminating the presence of confounders, but by balancing confounding equally across comparison groups

The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC primer on population health [Internet]. Assessing evidence and information. Available from https://phprimer.afmc.ca/en/part-ii/chapter-5

Interpreting Test Results

TP = True positive TN = True negative FP = False positive FN = False positive

		Disease	
		Present	Negative
Test Result	Positive	TP	FP
	Negative	FN	TN

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

Likelihood Ratio (LR)
- Likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
- LR+ indicates how much the probability of disease increases if the test is positive
- LR- indicates how much the probability of disease decreases if the test is negative

$$LR+ = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{[TP/(TP+FN)]}{[FP/(TN+FP)]} \qquad LR- = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{[FN/(TP+FN)]}{[TN/(TN+FP)]}$$

Positive Predictive Value (PPV)
- Proportion of people with a positive test who have the disease

$$PPV = \frac{TP}{TP + FP}$$

Negative Predictive Value (NPV)
- Proportion of people with a negative test who are free of disease

$$NPV = \frac{TN}{TN + FN}$$

		Advanced Neoplasia	
		Present	Negative
Test Result	Positive	68	147
	Negative	216	2234
	Total	284	2381

Sensitivity = 68/284 = 23.9%
Specificity = 2234/2381 = 93.8%

$$LR+ = \frac{0.239}{1 - 0.938} = 3.85 \qquad LR- = \frac{1 - 0.239}{0.938} = 0.81$$

$$PPV = \frac{68}{(68 + 147)} = 31.6\% \qquad NPV = \frac{2234}{(2234 + 216)} = 91.2\%$$

Figure 4. Interpreting test results: practical example using FOBT testing in advanced colon cancer
Source: Collins J, Lieberman D, Durbin T, et al. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med 2005;142:81-85

Figure 5. Understanding sensitivity and specificity
Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain. BMJ 2003;327:716-719

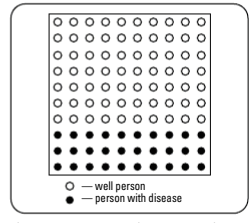


Figure 5a. Hypothetical population

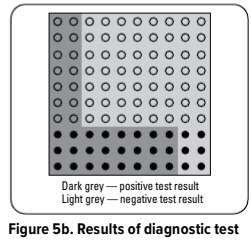


Figure 5b. Results of diagnostic test on hypothetical population

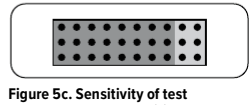


Figure 5c. Sensitivity of test (e.g. 24/30 = 80% sensitive)

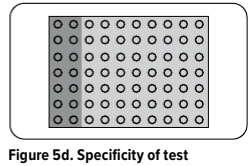


Figure 5d. Specificity of test (e.g. 56/70 = 80% specific)

Sensitivity
- proportion of people with disease who have a positive test

Specificity
- proportion of people without disease who have a negative test

Pre-Test Probability
- probability that a particular patient has a given disease before test/assessment results are known

Post-Test Probability
- a revision of the probability of disease after a patient has been interviewed/examined/tested
- post-test odds = pre-test odds × LR+, or, pre-test odds × LR-; for a positive test or negative test, respectively (recall odds = probability/(1-probability))
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
  - after each iteration, the resultant post-test probability becomes the pre-test probability when considering new investigations

Effectiveness of Interventions

Effectiveness, Efficacy, Efficiency
- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - **efficacy**: the extent to which a specific intervention produces a beneficial result under ideal conditions (e.g. RCT)
    - ideal conditions include adherence, close monitoring, access to health resources, etc.
  - **effectiveness**: measures the benefit of an intervention under usual conditions of clinical care
    - considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
  - **efficiency**: a measure of economy of an intervention with known effectiveness
    - considers the optimal use of resources (e.g. money, time, personnel, equipment)

Disease (e.g. lung cancer)

Exposure (e.g. smoking)	Present	Absent	Total
Present	A	B	A + B
Absent	C	D	C + D
Total	A + C	B + D	A + B + C + D

Case-Control Study

odds ratio (OR)* = $\frac{A}{C} \div \frac{B}{D} = \frac{A \times D}{B \times C}$

Cohort Study

$\frac{A}{A+B}$ = incidence rate of health outcome in exposed $\frac{C}{C+D}$ = incidence rate of health outcome in non-exposed

relative risk (RR)** = $\frac{A}{A+B} \div \frac{C}{C+D}$

attributable risk (AR)*** = $\frac{A}{A+B} - \frac{C}{C+D}$

*Ratio of the odds in favour of the health outcome among the exposed to the odds in favour among the unexposed
**Ratio of the risk of a health outcome among exposed to the risk among the unexposed
***Rate of health outcome in exposed individuals that can be attributed to the exposure

Figure 6. Measures of effect by study type

Number Needed to Treat (NNT)
- number of patients who need to be treated to achieve one additional favourable outcome
- only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility of intervention)
  - a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary
  - is equivalent to 1/Absolute Risk Reduction e.g. if the absolute difference in mortality between a group treated with drug A (where 40% of the patients die) and the placebo (where 50% of the patients die) is 10%, the NNT is 1/0.1 = 10 people needed to treat to prevent one death

Number Needed to Harm (NNH)
- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

- Sensitivity and specificity are characteristics of the test
- LR depends on the test characteristics, not the prevalence
- PPV and NPV depend on the prevalence of the disease in the population

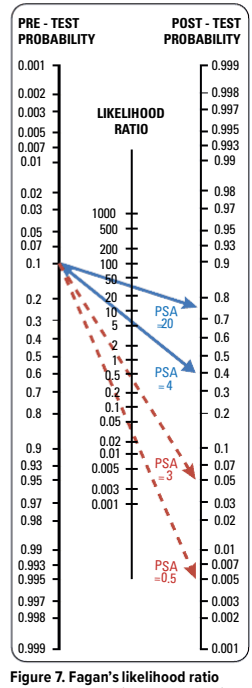


Figure 7. Fagan's likelihood ratio nomogram: practical example using PSA levels to calculate post-test probability of prostate cancer

Modified from source: Holmstrom B, Johansson M, Bergh A, et al. Prostate specific antigen for early detection of prostate cancer: longitudinal study. BMJ 2009;339:b3537

Equations to Assess Effectiveness

CER = control group event rate
EER = experimental group event rate
ARR = absolute risk reduction
RR = relative risk
NNT = number needed to treat
RR = EER/CER
ARR = CER – EER
NNT = 1/ARR

Beware

Do not be swayed by a large RR or odds ratio, as it may appear to be large if event rate is small to begin with. In these cases AR is more important (e.g. a drug which lowers an event which occurs in 0.1% of a population to 0.05% can boast a RR of 50%, and yet the AR is only 0.05%, which is not nearly as impressive)

Adherence (formerly compliance)
- degree to which a patient's behaviour and lifestyle concords with the recommendations of healthcare providers (e.g. the extent to which a patient takes medications as directed)

Coverage
- extent to which the services rendered cover the potential need for these services in a community

Sources: Shah, CP. Health indicators and data sources. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing Evidence and Information. AFMC Primer on Population Health

NNT
Consult http://www.thennt.com for quick summaries of evidence-based medicine (includes NNT, LR, and risk assessments)

Types of Study Design

Qualitative vs. Quantitative

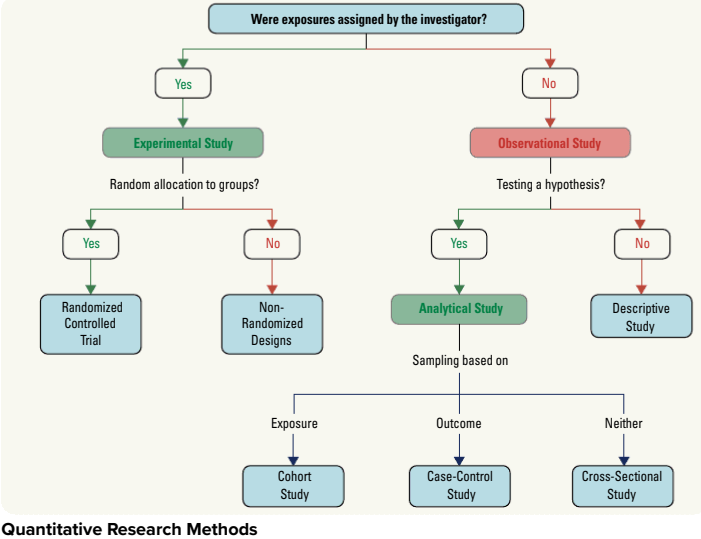
Formulating a Research Question

PICO
Population/**P**atient characteristics
Intervention/exposure of interest
Comparison group or control group
Outcome that you are trying to prevent or achieve

Table 6. Qualitative vs. Quantitative Study Designs

Qualitative	Quantitative
Often used to generate hypotheses (Why? What does it mean?)	Often tests hypotheses (What? How much/many?)
"Bottom-up" approach	"Top-down" approach
Observation → pattern → tentative hypothesis → theory	Theory → hypothesis → observation → confirmation
Sampling approach to obtain representative coverage of ideas, concepts, or experiences	Sampling approach to obtain representative coverage of people in the population
Narrative: rich, contextual, and detailed information from a small number of participants	Numeric: frequency, severity, and associations from a large number of participants

Source: Adapted from http://phprimer.afmc.ca
Source: The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing evidence and information. AFMC Primer on Population Health



Quantitative Research Methods

Figure 8. Quantitative study designs
Source: adapted from The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC Primer on Population Health [Internet]. About the primer on population health. Available from https://phprimer.afmc.ca/en/

Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study participants
- there are two main subtypes of observational studies: descriptive and analytic studies

Descriptive Studies

- describe the events and rates of disease with respect to person, place, and time; estimates disease frequency and time trends
- includes case reports, on one person or event, or a case series, which assesses exposures and outcomes
- can be used to generate an etiologic hypothesis and for policy planning

Analytic Studies

- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

An ecological fallacy is an erroneous conclusion made when extrapolating population level data to explain phenomena occurring in individuals. An example of an ecological fallacy would be concluding that red wine drinking leads to lower risk of death from CVS disease based on an ecological study showing that countries with a higher rate of red wine consumption have a lower rate of death from CVS causes

Table 7. Observational Study Designs

Type of Study	Ecological	Cross-Sectional	Case-Control	Cohort
Definition	Units of analysis are populations or groups of people, rather than individuals	Use individual data on exposures and outcomes gathered at the same time	Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)	Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor
Subjects	Aggregated groups (e.g. cities)	Sample of a population	Two or more samples of individuals with and without the outcome(s) of interest (i.e. cases and controls)	One or more cohorts Cohort: group of people with common characteristics (e.g. year of birth, region of residence) Divided into measured exposed vs. unexposed groups
Methods	Descriptions of the average exposure or risk of disease for a population Can use regression models to test associations between area-level predictors and aggregate outcomes	Collect information from each person at one particular time Tabulate the numbers in groups (e.g. by presence or absence of disease/factor of interest) Make tables and compare groups Estimate prevalence Use regression models to test associations between predictors and outcomes of interest	Select sample of cases of a specific disease during a specific time frame Representative of spectrum of clinical disease Select control(s) Represent the general population To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender) Assess past exposures (e.g. EMR, questionnaire) Association can be concluded between the risk factor and the disease (odds ratio)	Collect information on factors from all persons at the beginning of the study Subjects are followed for a specific period of time to determine development of disease in each exposure group Prospective: measuring from the exposure at present to the future outcomes Retrospective: measuring forward in time from exposures in the past to later outcomes Use statistical models to test associations between exposures and disease or other measured outcomes Provides estimates of incidence, relative risk, attributable risk
Advantages	Quick, easy to do Uses readily available data Generates hypothesis	Determines association between variables Quick and uses fewer resources Surveys with validated questions allows comparison between studies	Often used when disease in population is rare (less than 10% of population) due to increased efficiency or when time to develop disease is long Less costly and time consuming	Shows an association between risk factor(s) and outcome(s) Stronger evidence for causation Can consider a variety of exposures and outcomes
Disadvantages	Poor generalizability to individual level (not direct assessment of causal relationship) Ecological fallacy: an incorrect inference from groups to individuals Confounding	Does not allow for assessment of temporal relationship or offer strong evidence for causation between variables Confounding Selection bias Recall bias (see *Bias, PH14*)	Recall bias (see *Bias, PH14*) Confounding Selection bias for cases and controls Only one outcome can be measured	Confounding may occur due to individuals self-selecting the exposure, or unknown/unmeasured factors are associated with the measured exposure and outcome Cost and duration of time needed to follow cohort Selection bias
Examples	A study looking at the association between smoking rates and lung cancer rates in different countries at the population level without individual data on both factors	A study that examines the distribution of BMI by age in Ontario at a particular point in time	A famous case control study published by Sir Richard Doll demonstrated the link between tobacco smoking exposure and lung cancer cases at the individual level	A famous cohort study is the Framingham Heart Study, which assessed the long-term cardiovascular risks of diet, exercise, and medications such as ASA, etc.

Sources: Shah, CP. Measurement and investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003.
The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC primer on population health [Internet]. Assessing evidence and information. Available from https://phprimer.afmc.ca/en/part-ii/chapter-5/
Rothman KJ, Greenland SG, Lash TL. Modern epidemiology, 3e. Philadelphia: Wolters Kluwer, 2012.

Experimental Study Designs

- not discussed here are non-randomized controlled trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible)

RANDOMIZED CONTROLLED TRIAL (RCT)

Definition
- participants are assigned by random allocation to two or more groups, one of which is the control group and the other group(s) receive(s) an intervention

Participants
- individuals are selected using explicit inclusion/exclusion criteria and recruitment targets are guided by sample size calculations

Methods
- random allocation of individuals into two or more treatment groups through a centralized concealed process
- method of assessment to reduce bias
  - **single-blind**: participant does not know group assignment (intervention or placebo)
  - **double-blind**: participant and observer both unaware of group assignment
  - **triple-blind**: participant, observer, and analyst unaware of group assignment
- control group receives standard of care or placebo if no standard of care exists
- one or more group(s) receive(s) the intervention(s) under study
- baseline covariate(s) and outcome(s) are measured and the groups are compared
- all other conditions are kept the same between groups

Advantages
- "gold standard" of studies, upon which the practice of EBM is founded
- provides the strongest evidence for effectiveness of intervention
- threats to validity are minimized with sufficient sample size and appropriate randomization
- randomization is one of few methods that can eliminate confounding (including unmeasured confounders) and self-selection bias
- allows prospective assessment of the effects of intervention

Disadvantages
- some exposures are not amenable to randomization (e.g. cannot randomize participants to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
- can be difficult to randomly allocate groups (e.g. communities, neighbourhoods)
- difficult to study rare events since RCTs require extremely large sample sizes
- contamination, co-intervention, and loss to follow-up can all limit causal inferences
- can have poor generalizability (e.g. when trial participants are healthier than the average patient population)
- costly

Shah, CP. Measurement and investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003.
The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC primer on population health [Internet]. Assessing evidence and information. Available from https://phprimer.afmc.ca/en/part-ii/chapter-5/

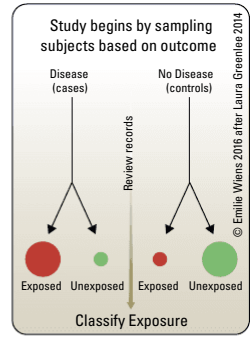


Figure 9. Case-control study
Adapted from http://phprimer.afmc.ca

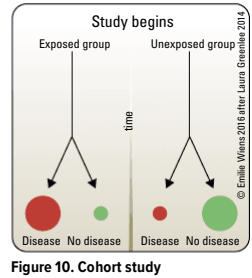


Figure 10. Cohort study
Adapted from http://phprimer.afmc.ca

Analysis
Per-Protocol Analysis (PP)
Strategy of analysis in which only patients who complete the entire study are counted towards the results

Intention-to-Treat Analysis (ITT)
When groups are analyzed exactly as they existed upon randomization (i.e. using data from all patients, including those who did not complete the study)

An example of an RCT is the SPARCL trial, which demonstrated intense lipid-lowering with atorvastatin reduces the risk of cerebrovascular and cardiovascular events in patients with and without carotid stenosis when compared to placebo

An example of a meta-analysis is one that compares the effects of ACEIs, calcium channel blockers, and other antihypertensive agents on mortality and major cardiovascular events by compiling and analyzing data from a full set of reported RCTs

Summary Study Designs

META-ANALYSIS

Definition
- a form of statistical analysis that aggregates all relevant studies addressing the same research question in order to increase statistical precision

Participants
- all the studies identified through a systematic literature review

Methods
- selection of relevant studies from the published literature which meet quality criteria
- statistical models used to combine the results of each independent study
- provides a summary statistic of overall results as well as graphic representation of included studies (forest plot)

Advantages
- attempts to overcome the problem of reduced power due to small sample sizes of individual studies
- can address questions (e.g. subgroup analyses) that the original studies were not powered to answer

Disadvantages
- studies may be heterogeneous and therefore inappropriate to combine (e.g. different patient populations, exposure classification/measurement, outcome assessment)

- reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)

Shah, CP. Measurement and investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003.
The Association of Faculties of Medicine of Canada Public Health Educators' Network. AFMC primer on population health [Internet]. Assessing evidence and information. Available from https://phprimer.afmc.ca/en/part-ii/chapter-5/

Methods of Analysis

Distributions

- a distribution describes the frequency at which each value (or category) occurs in a study population
- distributions can take characteristic shapes (e.g. normal (Gaussian) or non-normal (binomial, gamma, etc.))
- characteristics of the normal distribution
  - mean = median = mode
  - 68% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - mean: sum of each observation's data (e.g. ages) divided by total number of observations
  - median: value of the 50th percentile; a better reflection of the central tendency for a skewed distribution
  - mode: most frequently observed value in a series
- measures of dispersion
  - range: the largest value minus the smallest value
  - variance: a measure of the spread of data
  - standard deviation: the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal distribution curve, a description of the entire distribution of data is obtained

Consult the Cochrane Library of Systematic Reviews (http://www.cochranelibrary.com) for high-quality systematic reviews and meta-analyses

Example Calculation
Data set: 17, 14, 17, 10, 7
Mean = (17 + 14 + 17 + 10 + 7) ÷ 5 = 13
Median (write the list in order, median is the number in the middle) = 7, 10, 14, 17, 17 = 14
Mode (number repeated most often) = 17
Range = 17 – 7 = 10
Variance = $[(17-13)^2 + (14-13)^2 + (17-13)^2 + (10-13)^2 + (7-13)^2] \div (5-1) = 19.5$
Standard Deviation = √variance = √19.5 = 4.42

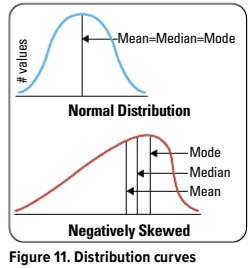


Figure 11. Distribution curves

Data Analysis

Statistical Hypotheses

- null (Ho)
  - the default hypothesis; often states there is no relationship between two variables
- alternative (H1)
  - the hypothesis that we are interested in; often states there is a relationship between two variables
  - we can find evidence against Ho but we can never 'prove' H1

Type I Error (α Error)

- the null hypothesis is falsely rejected (i.e. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error since a type I error can have larger clinical significance than a type II error
- e.g. in a study exploring a drug's effectiveness on lowering blood pressure, the data may indicate the drug is effective and therefore lowers blood pressure, when in reality the drug is ineffective

Type I (α) Error
"There Is **A**n **E**ffect" where in reality there is none

Type II Error (β Error)

- the null hypothesis is falsely accepted (i.e. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- by convention a higher level of beta error is often accepted for most studies in comparison to alpha error
- can also be used to calculate statistical power
- e.g. in a study exploring the effectiveness of a COVID-19 vaccine, the data suggests the vaccine is ineffective and therefore does not protect against COVID-19 infection, when in reality it does

Power

- probability of correctly rejecting a null hypothesis when it is, in fact, false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
- power increases with an increase in sample size
- power = 1 – β, and is therefore equal to the probability of a true positive result

Statistical Significance

- the probability that the statistical association found between variables is due to random chance alone (i.e. there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently $p<0.05$
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (denoted by the α-value)

Clinical Significance
- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient adherence, and side effects in addition to statistical significance

Confidence Interval (CI)
- provides a range of values, bound by the upper and lower confidence limits, that contains the true population parameter (e.g. the mean)
- frequently reported as 95% CI (e.g. if this study were repeated 100 times, the 95% confidence interval would contain the populate parameter 95 out of 100 times)

Data
- there are 2 types of quantitative data
  - continuous data (e.g. height in cm)
  - discrete data (e.g. number of patients in the ICU)
- information collected from a sample of a population
- there are 4 overall levels of measurement for quantitative data
  - categorical (e.g. blood type, marital status)
  - ordinal (e.g. low, medium, high)
  - interval (e.g. °C, time of day)
  - ratio (e.g. serum cholesterol, hemoglobin, age)

Validity/Accuracy (of a measurement tool)
- how closely a measurement reflects the entity it claims to measure

Reliability/Precision
- how consistent multiple measurements are when the underlying subject of measurement has not changed
- may be assessed by different observers at the same time (inter-rater reliability) or by the same observer under different conditions (test-retest reliability)

Internal Validity
- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the reliability, accuracy, and absence of other biases

External Validity (i.e. Generalizability)
- degree to which the results of the study can be generalized to other situations or populations

A wider confidence interval implies more variance than a tighter confidence interval given the same critical value

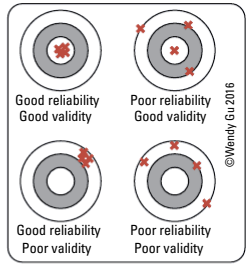


Figure 12. Validity vs. reliability

What's the difference between Pearson and Spearman correlation?
Different types of correlation are used for different levels of measurement. Pearson is for continuous and normal data, Spearman is for ordinal or non-normal data. There are other forms of correlation for other levels of measurement (e.g. tetrachoric/polychoric)

Common Statistical Tests

Table 8. Statistical Tests

	Two Sample Z-Test	Analysis of Variance (ANOVA)	Chi-Squared Test ($\chi 2$)	Linear Regression	Logistic Regression	Pearson Product-Moment Correlation (Pearson's r)
What are you trying to show?						
	Compare the mean values of an outcome variable between two groups (e.g. difference in average BP between men and women)	Compare the mean values of an outcome variable between two or more groups (e.g. difference in average BP between persons in three towns)	Tests if two categorical variables are independent or not (e.g. association between family history of breast cancer and having breast cancer)	Model relationship between a continuous variable and one or more explanatory variables	Model relationship between a categorical variable and one or more explanatory variables	Assesses the strength of the linear relationship between two variables. Ranges from -1 (perfect negative association, increases in one variable are associated with decreases in another) to 1 (perfect positive association, increases in one variable are associated with increases in the other). A correlation of 0 indicates no relationship
What kind of variables do you measure?						
Dependent Variable	Continuous	Continuous	Categorical (2 or more)/ordinal	Continuous	Categorical (outcomes usually dichotomous)	Continuous
Independent Variable	Dichotomous	Categorical/Ordinal (2 or more)	Categorical/Ordinal (2 or more)	Continuous/Ordinal/ Categorical	Continuous/Ordinal/ Categorical	Continuous
Assumptions	Data follow a normal/t-distribution Equal variances Data are independent	Normal distribution of dependent variable's error term Data are independent	Expected counts must be at least 5 for all cells in n by n table Data are independent	Dependent variable's error term has normal distribution Linear relationship between variables Homoscedasticity No influential values Data are independent	Linearity (on logit scale) No influential values Model has adequate goodness-of-fit Data are independent	Underlying relationship is linear Data for both variables are normally distributed Data are independent

Causation

Criteria for Causation (Bradford Hill Criteria)

1. **strength of association**: the frequency with which the factor is found in the disease and the frequency with which it occurs in the absence of disease
2. **consistency**: is the same relationship seen with different populations or study design?
3. **specificity**: is the association particular to your intervention and measured outcome?
4. **temporal relationship**: did the exposure occur before the onset of the disease?
5. **biological gradient**: finding a dose-response relationship between the exposure-outcome
6. **biological plausibility**: does the association/causation make biological sense?
7. **coherence**: can the relationship be explained/accounted for based on what we know about science, logic, etc.?
8. **experimental evidence**: does experimental evidence support the association (e.g. is there improvement?)
9. **analogy**: do other established associations provide a model for this type of the relationship?

Note: Not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes 'experimental evidence' as superior to other criteria for experimental causation review. However, many causation questions in health cannot be answered with experimental methods

Source: Bradford Hill A. The environment and disease: association or causation. Proc R Soc Med 1965;58(5):295-300

Assessing Evidence

- critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision

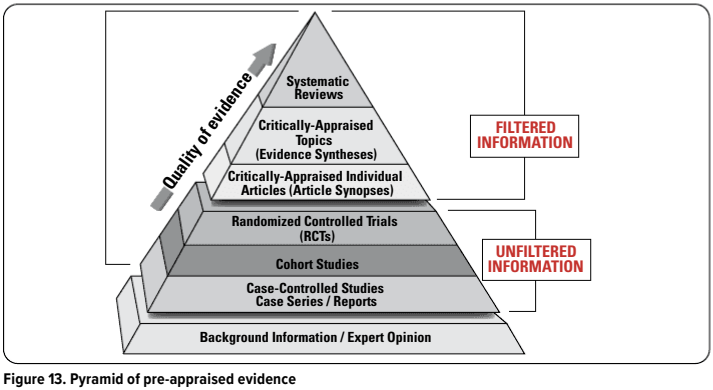


Figure 13. Pyramid of pre-appraised evidence

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A. Are the results of the study valid?
- see below for classifications of evidence that has already been assessed

B. What are the results?
- what was the impact of the treatment effect?
- how precise was the estimate of treatment effect?
- what were the confidence intervals and power of the study?

C. Will the results help me in caring for my patients?
- are the results clinically significant?
- can I apply the results to my patient population?
- were all clinically important outcomes considered?
- are the likely treatment benefits worth the potential harm and costs?

Levels of Evidence: Classifications Cited in Guidelines/Consensus Statements

Level I evidence: based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results

Level II evidence: based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results

Level III evidence: based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies

Level IV evidence: based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines

Level V evidence: opinions of the individuals who have written/reviewed the guidelines (i.e. Level IV evidence), based on experience/-knowledge of literature/peer discussion

Notes: These 5 levels of evidence are not direct evaluations of evidence quality or credibility; they reflect the nature of the evidence. While RCTs tend to be most credible (with <III), level III evidence gains credibility when multiple studies from different locations and/or time periods report consistent findings. Level IV and V evidence reflects decision-making that is necessary but in the absence of published evidence.

Figure 14. Levels of evidence classifications
Note: This is only one method of classifying evidence. Various systems exist, but operate within the same premise that certain types of evidence carry more weight than others

Health System Planning and Quality

Continuous Quality Improvement

Quality Improvement (QI)
- a means of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to cause variation in quality
- measures to increase efficiency of action with the purpose of achieving optimal quality

Implications for Patient Safety
- quality improvement plays a crucial role in enhancing patient safety in healthcare organizations, such as: identifying and reducing medical errors, adverse events, infections, and harms associated with healthcare delivery
- effective QI can contribute towards reducing morbidity and mortality rates, and improving patient outcomes
- implementation of QI initiatives also contributes to a culture of safety. Examples include checklists, guidelines, standardized procedures/protocols

Quality Assurance
- process to guarantee the quality of health care through improvement and attainment of set standards
- "five-stage process of quality assurance"

Source: Shah, CP. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003

1. formulation of working goals
2. procedural changes to implement those goals
3. regular comparison of current performance with original goals
4. development of solutions to bring performance closer to goals
5. documentation of quality assurance activities

Quality Control
- a process of surveying the quality of all factors involved in the process to maintain standards

Continuous Quality Improvement
- the process of ongoing service/product refinement via the vigilant review of expectant issues detrimental to the system and regular incorporation of improvements

Quality Management
- combination of several processes (assurance, control, improvement) to maintain consistent quality

Total Quality Management
- management principle for advancing quality while minimizing additional expenditures
- focuses on the entire system rather than discrete elements

Audit
- methodical analysis of a quality system by quality auditors
- to determine whether quality processes and results comply with goals and whether processes have been implemented effectively

Systems Analysis Tools

1. **5 Whys**: brainstorming to simplify the process of change; continue asking 'why' until the root of the problem is discovered
2. **Ishikawa Diagrams** (i.e. Fishbone Diagrams): identify generic categories of problems that have an overall contribution to the effect
3. **Defect Check Sheets**: consider all defects and tally up the number of times the defect occurs
4. **Pareto Chart**: x vs. y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis; purpose is to highlight most important among large set of factors contributing to defects/poor quality

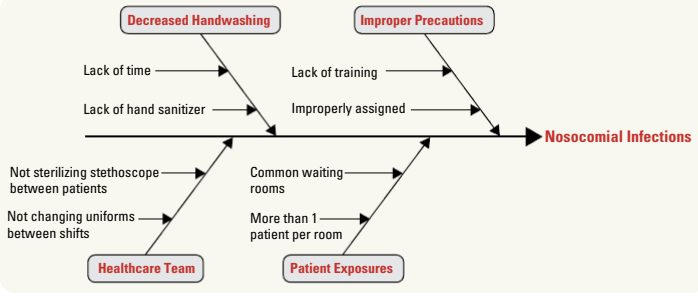

Figure 15. Ishikawa diagram

Precede-Proceed Model

- tool for designing, implementing, and evaluating health interventions/programs

Table 9. Precede-Proceed Model

PRECEDE Phase	PROCEED Phase
Phase 1 – Identify the ultimate desired result	Phase 5 – Implementation (design and conduct the intervention)
Phase 2 – Identify health issues and their behavioural and environmental determinants. Set priorities among them	Phase 6 – Process evaluation (determine if the program is implemented as planned)
Phase 3 – Identify the predisposing, enabling, and reinforcing factors that affect the behaviours and environmental determinants	Phase 7 – Impact evaluation (measure intermediate effects on the target population)
Phase 4 – Identify the administrative and policy factors that influence what can be implemented	Phase 8 – Outcome evaluation (determine whether the original desired result was achieved)

Planning Cycles/Models

1. **APIE Planning Model**: *Assessment, Planning, Implementation, Evaluation*
2. **PDSA Planning Cycle**: *Plan, Do, Study, Act*

Economic Evaluation

Cost Benefit Analysis (CBA)

- an analysis which compares the total expected costs with the total expected benefits of actions in order to choose the most profitable or beneficial option(s)
- costs are controlled for inflation and market changes so that the effect of the change is evaluated over a consistent, preset financial value

Cost Effectiveness Analysis (CEA)

- ratio of change in cost (numerator) to change in effect (denominator) in response to a new strategy or practice
  - the numerator highlights the cost of the health gain
  - some examples of changes in effect (denominator) could be years of life gained or sight-years gained
  - the most commonly used outcome measure is quality-adjusted life years (QALY) (see *Quality Adjusted Life Year, PH13*)
- can be used where an extensive cost benefit analysis is not applicable or appropriate

Cost Utility Analysis (CUA)

- special case of CEA where effectiveness is measured in utility, commonly in quality-adjusted life years (QALY)
- **Note**: term is sometimes used interchangeably with CEA

Managing Disease Outbreaks

Definitions

Outbreak
- incidence of new cases beyond the usual frequency of disease in a population or community in a given time

Endemic
- consistent existence of infectious agent or disease in a given population or area (i.e. usual rate of disease)

Epidemic
- an increase, often sudden, in cases of a disease above what is usually expected in a particular population (e.g. SARS epidemic)
- can occur due to a recent increase in the virulence or amount of an agent, introduction of a new agent to an area, enhanced mode of transmission of the agent, altered host response, and/or increased host susceptibility through more exposure or portals of entry

Pandemic
- epidemic that has spread across international or intercontinental boundaries, affecting a large number of people (e.g. COVID-19 pandemic)

Attack Rate
- proportion of an initially disease-free population that develops the disease over a specified time period
- = [(# of new cases of disease) / (initial population size)] * 100%

Secondary Attack Rate
- the proportion of individuals who develop disease as a result of exposure to primary contacts during the incubation period
- = [(total # of cases - initial # of cases) / (# of susceptible individuals - initial # of cases)] * 100%
- measure of infectiousness, which reflects the ease of disease transmission

Virulence
- measure of an infectious agent to cause significant sickness
- = (# of cases that are severely ill or died) / (total # of cases)

Case-Fatality Rate (CFR)
- proportion of individuals with the disease who died as a result of the illness during a specified time period
- must be clearly differentiated from the mortality rate

Mortality Rate
- proportion of the population that died from any cause during a specified time period
- crude mortality rate (unadjusted for age)

Basic Reproduction Number (R0)
- the average number of secondary infections that arise from one infection
- can only be calculated in a susceptible population

Steps to Control an Outbreak

Infection Control Precautions

Contact (e.g. impetigo, chicken pox, warts)
- wash hands
- gloves
- gown
- wipe equipment after use

Droplet (e.g. influenza, mumps, pneumonia)
- contact precautions PLUS
- goggles/face shield
- surgical mask

Airborne (e.g. TB)
- contact precautions PLUS
- N95 mask (fit-tested)
- negative pressure room

COVID-19 precautions
Precautions include hand hygiene, gown, eye protection, and well-fitting masks (e.g. surgical mask). N95 respirators are reserved for aerosol-generating procedures, such as endotracheal intubation and bronchoscopy
For specific examples, see "Communicable Diseases" section in: Shah CP. Public health and preventive medicine in Canada. 5th ed. Toronto: Elsevier; 2003
Source: Public Health Ontario: https://www.publichealthontario.ca/-/media/documents/ncov/ipac/ipac-additional-precautions-acute-care.pdf?la=en

Active Surveillance
Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection)

Passive Surveillance
A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered)

Canada's Response to the COVID-19 Pandemic
- In late 2019, the novel coronavirus (COVID-19) led to a global pandemic
- By May 2020, there were over 70000 cases in Canada and more than 4.3 million cases worldwide
- Symptoms of the virus varied from dry cough, fever, and fatigue, to more severe respiratory symptoms such as dyspnea and chest pain
- PHAC developed the following response:
  - Development and implementation of new diagnostic tests based on the genetic sequence of COVID-19
  - Prompt identification, risk assessment, management, and placement of confirmed cases by healthcare professionals
  - Application of routine practices and additional precautions for healthcare workers: gloves, long-sleeved gowns, facial protection, and masks
  - Enforcement of national physical distancing protocols and 14-day self-isolation for those returning from international travel
  - Free vaccines against COVID-19 were made available to everyone in Canada over the course of 2021
  - The temporary closure of many institutions and reduction in income for millions of Canadians resulted in novel social assistance programs, such as the Canada Emergency Response Benefit

Source: Government of Canada. Coronavirus (COVID-19): Canada's Response [Internet]. Ottawa (ON): Government of Canada; 2020 [updated 2022 Mar 29; cited 2022 Apr 27]. Available from: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/canadas-reponse.html

Table 10. Ten-Step Approach

Steps	Details
1. Identify the investigation team and resources	Local public health units (e.g. Toronto Public Health) Federal level (e.g. PHAC)
2. Establish existence of an outbreak	Compare the number of cases during the suspected outbreak to the number of cases expected during a non-outbreak time frame (e.g. receiving a report of a vomiting baseball team after a team dinner at a restaurant)
3. Verify the diagnosis	Obtain medical records and lab reports Conduct further clinical testing as needed
4. Define a case	3 components: Person, Place, Time (e.g. "Diagnosis A: Person with XYZ signs and symptoms… Occurred after visiting X… During months/year")
5. Find cases systemically and create a line listing	A line listing should include clinical information (signs/symptoms, onset times/dates), demographic information, exposure information
6. Perform descriptive epidemiology and develop hypotheses	Create epidemic curves (see *Figure 16*)
7. Evaluate hypotheses and conduct additional studies as needed	Case-control studies: useful when not everyone exposed can be found and included in the study Cohort studies: useful when all persons exposed can be included in the study
8. Implement control measures	Can occur at any stage in an outbreak (e.g. isolation)
9. Communicate findings	Involve the media to address public concerns and call for public action
10. Continue surveillance	Determine when the outbreak is over Document the effectiveness of control measures

Source: Adapted from Moore Z. Outbreak Investigations: The 10-Step Approach [Internet]. North Carolina: Government of North Carolina; [updated 2019 Dec 16; cited 2020 Jun 20]. Available from: https://epi.dph.ncdhhs.gov

Infection Control Targets

- interventions should target host, agent, environment, and their interactions

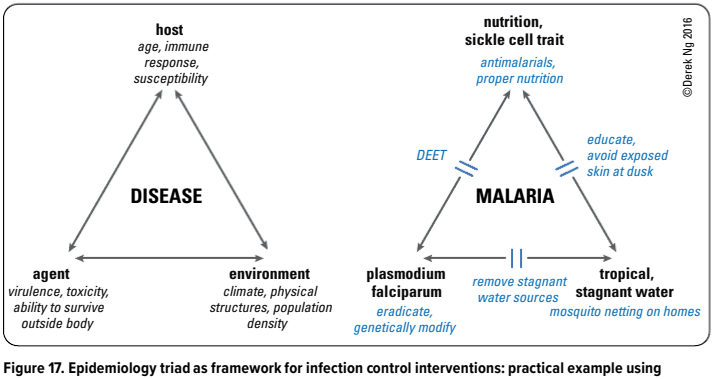

Figure 17. Epidemiology triad as framework for infection control interventions: practical example using malaria

The International Health Regulations (IHR)

- an international agreement involving 196 nations to prevent, protect against, control, and provide a public health response to pandemics
- a public health emergency of international concern (PHEIC) is "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response"
- the IHR Emergency Committee provides the WHO Director-General with temporary recommendations on PHEIC events

Reducing Inequities During the COVID-19 Pandemic
Public Health Rev 2022;42:1604031
This review outlines public health recommendations during the COVID-19 Pandemic including primordial, primary, secondary, and tertiary prevention strategies

Figure 16. Epidemic curves

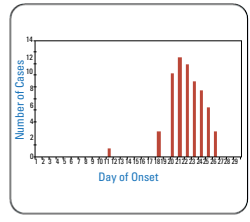

Figure 16a. Point source epidemic curve

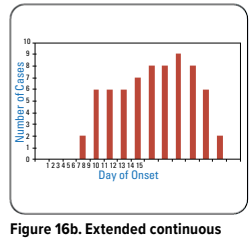

Figure 16b. Extended continuous source epidemic curve

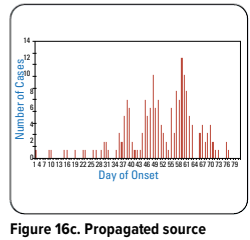

Figure 16c. Propagated source epidemic curve

Environmental Health

Definition
- study of the association between environmental factors (both constructed and natural) and health
- environmental exposures
  - four common hazards: chemical, biological, physical, and radiation
  - four main reservoirs: air, food, water, and soil
  - three main routes: inhalation, ingestion, or absorption (skin)
- usually divided into two main settings
  - workplace (including schools): may see high level exposure in healthy individuals (see *Occupational Health, PH29*)
  - non-workplace: lower levels of exposure over a longer period of time; affects vulnerable populations more severely, such as at extremes of age, and the immunosuppressed; may be teratogenic
- health impacts of the environment also include factors (e.g. urban planning) and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths can facilitate more active lifestyles)

Table 11. Environmental Health Jurisdiction

Public Health Unit	Enforcement of water and food safety regulations (including restaurant food safety) Assessment of local environmental risks Monitoring and follow-up of reportable diseases Investigation of environmental contamination, clusters of disease
Municipal Government	Waste disposal, recycling, water and sewage treatment/collection/distribution
Provincial and Territorial Government	Water and air quality standards Industrial emission regulation Toxic waste disposal
Federal Government	Designating and regulating toxic substances Regulating food products (e.g. Health Canada (drugs), Canadian Food Inspection Agency (CFIA)) Setting policy for pollutants that can travel across provincial boundaries
International	Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change, International Joint Commission)

Source-Path-Receiver Model
- to prevent workplace injuries, strategies can be implemented to improve the safety profile of the source, modify the path, and/or protect the receiver

Environmental Risk Assessment

Hazard Identification and Risk Assessment (HIRA)

Hazard Identification
- what is the hazard involved?
- assess potential hazards by taking environmental health history

Risk Characterization
- is the identified agent likely to elicit the patient's current symptoms?
- review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. evaluate hazard threshold levels)

Exposure Assessment
- is the patient's exposure to the environmental agent sufficient to have caused the current symptoms?
- quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard

Adapted from p.250, Sixth Edition of A Dictionary of Epidemiology by Miquel Porta

Air

Biological Hazards
- moulds thrive in moist areas; 10-15% of the population is allergic
- bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. Legionella)
- dust mites (yr-round) and pollens (seasonal) can trigger upper- and lower-airway symptoms

Chemical Hazards
- ground-level ozone
  - main component of smog with levels increasing in major cities
  - worsens asthma, irritates upper airway

Environmental Health Jurisdiction - Taking an Environmental Health History
CMAJ 2002; 166(8):1049-1055

CH2OPD2
Community
Home
Hobbies
Occupation
Personal habits
Diet
Drugs

BPA, The Toxin Concern of 2009
Bisphenol A (BPA) is a chemical compound found in some hard, clear, lightweight plastics and resins. According to the NIH, animal studies suggest that ingested BPA may imitate estrogen and other hormones. In October 2008, Canada became the first country in the world to ban the import and sale of polycarbonate baby bottles containing BPA, stating that although exposure levels are below levels that cause negative effects, current safety margins need to be higher. The US FDA does not consider normal exposure to BPA to be a hazard, however the NIH has some concern that fetuses, infants, and children exposed to BPA may be at increased risk for early-onset puberty, prostate, and breast cancer

Cannabis Legalization and Driving Under the Influence of Cannabis (DUIC)
Source: Public Health Ontario. Evidence Brief-Driving Under the Influence of Cannabis, 2017
Since the Government of Canada stated its commitment to legalize cannabis via the Cannabis Act (Bill C-45) on April 13, 2017, the Canadian Task Force on Cannabis Legalization and Regulation specifically noted driving impairment as an important consideration. Higher cannabis use, cannabis-dependence, lower perceived risk from DUIC, and normative beliefs about DUIC were identified as risk factors. As such, an act to amend the Criminal Code Bill C-46 was simultaneously introduced to enable the police to request an oral fluid sample for roadside drug screening and to implement THC per se whole blood limits (>2 ng/mL punishable). Public health was also advised to devise population-based interventions such as 6 hour waiting period recommendations before driving, as well as preventive strategies through addiction services, mass-media campaigns, and school-based instructional programs

- carbon monoxide (fossil fuel-related, common byproduct of combustion)
  - aggravates cardiac disease at low levels
  - headache, nausea, dizziness at moderate levels
  - fatal at high levels
- sulphur dioxide (fossil fuel-related), nitrogen oxides
  - contribute to acid rain and exacerbate breathing difficulties
- organic compounds at high levels (e.g. benzene, methylene chloride, tetrachloroethylene)
  - tend to be fat-soluble, easily absorbed through skin, and difficult to excrete
- heavy metal emissions (e.g. nickel, cadmium, chromium)
  - variety of health effects: upper airway disease, asthma, decreased lung function
- second-hand tobacco smoke
  - respiratory problems, increased risk of lung cancer
  - particulates associated with decreased lung function, asthma, upper airway irritation

Radiation Hazards

- ionizing radiation
  - radon is naturally produced by soil containing uranium or radium; can contaminate indoor air associated with ~20% of lung cancers
- non-ionizing radiation
  - visible light, infrared, microwave
  - increasing ultraviolet radiation from ozone layer destruction increases risk of skin cancer

Water

Biological Hazards

- mostly due to human and animal waste
- Indigenous peoples, Black Nova Scotians, and rural Canadians at higher risk
- bacteria: *Escherichia coli* (e.g. Walkerton, ON), Salmonella, Pseudomonas, Shigella
- protozoa: Giardia, Cryptosporidium (e.g. North Battleford, SK)

Chemical/Industrial Hazards

- chlorination by-products (e.g. chlorinated water can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides, and other industrial waste products can be present in groundwater
- mercury from fish (exposure during pregnancy can be neurotoxic for the fetus)
- asbestos (e.g. from old buildings)
- lead (can be found in paint, older buildings, and traditional medicines in dangerous quantities)

Soil

Biological Hazards

- biological contamination: tetanus, Pseudomonas

Chemical Hazards

- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, residue of industrial waste/development (e.g. urban agriculture), lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- infants and toddlers at highest risk of exposure due to hand-mouth behaviours
- effects dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue

Estimates and 25-year Trends of the Global Burden of Disease Attributable to Ambient Air Pollution
Lancet 2017;389:1907-1918
Purpose: To determine global, regional, and country-level trends in mortality and disease burden due to ambient air pollution from 1990-2015.
Methods: Satellite-based estimates, chemical transport models, and group-level measurements were used to estimate global population-weighted mean concentrations of particle mass with aerodynamic diameter less than 2.5 μm (PM2.5) and ozone.
Results: In 2015, PM2.5 ranked 5th for factors causing mortality and led to 4.2 million deaths and 103.1 million disability-adjusted life years (DALYs). Ozone-induced COPD resulted in an additional 254,000 deaths and loss of 4.1 million DALYs.
Conclusion: Ambient air pollution is an increasing global disease burden resulting in substantial morbidity.

Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement from the American Heart Association
Circulation 2010;121(21):2331-2378
A scientific statement by the American Heart Association in 2004 reported that exposure to particulate matter air pollution contributes to cardiovascular morbidity and mortality. An updated American Heart Association statement in 2010 confirmed a causal relationship between particulate matter exposure and cardiovascular morbidity and mortality. The statement reported that such an exposure over several h to wk may trigger cardiovascular disease-related mortality and non-fatal events, whereas longer exposures over several yr may further increase cardiovascular mortality risk and reduce life expectancy within highly-exposed populations by several mo to yr

The Walkerton Tragedy
In May 2000, the drinking water system in the town of Walkerton, ON, became contaminated with *Escherichia coli* O157:H7 and *Campylobacter jejuni*. Over 2300 individuals became ill; 27 people developed hemolytic uremic syndrome and 7 individuals died in the outbreak
Source: Ministry of the Attorney General. Report of the Walkerton inquiry. Ontario, 2002

Water Fluoridation
Water fluoridation, and the resulting decrease in dental caries and reduction in health inequities, is one of the greatest public health achievements of the 20th century. At the recommended concentration of 0.7 mg/L, fluoride reduces cavities by 18-40%. Small but vocal groups opposed to fluoridation have claimed that fluoride intake is not easily controlled, and that children may be more susceptible to health problems. These claims have been widely debunked but still persist, and have led some communities to opt not to fluoridate their water, resulting in increased dental caries (e.g. Calgary). Fluoride concentrations in municipal water should be 0.7 ppm

Food

Biological Hazards

Table 12. Comparison of Select Biological Contaminants of Food and Effects on Human Health

	Source	Effects
Salmonella	Raw eggs, poultry, meat	GI symptoms
Campylobacter	Raw poultry, raw milk	Joint pain, GI symptoms
Escherichia coli	Various including meat, sprouts Primarily undercooked hamburger meat	Watery or bloody diarrhea Hemolytic uremic syndrome (especially children)
Listeria monocytogenes	Unpasteurized cheeses, prepared salads, cold cuts	Listeriosis: nausea, vomiting, fever, headache, rarely meningitis or encephalitis
Clostridium botulinum	Unpasteurized honey, canned foods	Dizziness, weakness, respiratory failure GI symptoms: thirst, nausea, constipation
Prion (BSE*)	Beef and beef products	Variant Creutzfeldt-Jakob disease

*BSE = bovine spongiform encephalopathy

- other biological food contaminants include:
  - viruses, mould toxins (e.g. aflatoxin has been associated with liver cancer), parasites (e.g. *Toxoplasma gondii*, tapeworm), paralytic shellfish poisoning (rare), genetically modified organisms (controversial as to health risks/benefits)

Chemical Hazards

- many persistent organic pollutants are fat-soluble and undergo bioamplification
- drugs (e.g. antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrites highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
- pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects (e.g. dermatological, gastrointestinal, neurological, carcinogenic, respiratory, reproductive, and endocrine effects)
- polychlorinated biphenyls (PCBs)
  - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally-exposed individuals than in the general population
- dioxins and furans
  - levels highest in fish and marine mammals, also present in breast milk
  - can cause immunosuppression, liver disease, and respiratory disease

Examples of Simple Interventions to Reduce Environmental Exposures and Risk of Disease

- sunscreen to prevent sunburns and UV-related damage
- ear plugs to prevent damage from high intensity sound waves

Organic Foods

Foods designated as "organic" in Canada must conform to the Organic Products Regulations enforced by the Canadian Food Inspection Agency

Organic foods are not free of synthetic pesticide residues but typically contain smaller amounts compared to conventionally grown foods

Currently, there has not been strong evidence to suggest that eating organic foods is safer or more nutritious compared to eating conventionally grown food

Sources: Organic foods. Ann Intern Med 2012;157:348-366. Health Canada. Pesticides and food, 2011. UpToDate. Organic foods and children, 2009

Environmental Racism

- defined as the deliberate and disproportionate development of environmental hazards and toxic facilities near communities without a strong voice (Indigenous, immigrant, racialized groups, and lower SES)
- furthermore, historic and present-day colonialist and racist practices contribute to the marginalization of these communities, resulting in a diminished organizational capacity and political power to advocate against the placement and impacts of these environmental hazards
- exposure to these environmental hazards therefore undergird to poorer health outcomes and marginalization already faced by affected individuals and communities - can also impact livelihood (e.g. fishing, agriculture, hunting, trapping)
- examples of environmental racism in Canada are ubiquitous against Indigenous communities and communities of colour. Present-day examples include: the placement of oil and gas industries across Indigenous lands without invitation, engagement and permissions; a lack of access to potable water, as seen in communities such as Attawapiskat, Ontario; and other environmental hazards, with two specific examples provided below

Grassy Narrows, Ontario

- a reserve in northwest Ontario, which came to public attention in the 1970s when many of its residents began to develop symptoms of mercury poisoning, including severe neurotoxicity
- the source of contamination was attributed to an upstream paper mill dumping tonnes of untreated mercury into the water over a period of several years

- a loss of natural resources and environmental stewardship had a devastating pervasive impact on the community:
  - the decimation of two major sources of employment in the area (fishing and working as guides)
  - contamination of local food and water supplies
  - leaving the community with limited resources to manage the short- and long-term effects of mercury poisoning
- despite ongoing protest, agreement from the federal government to build a mercury treatment facility was not reached until 2020, approximately 50 years following the initial contamination of Grassy Narrows. At time of writing, construction of such a facility had yet to begin
- despite the federal government's promise to eliminate drinking water advisories on reserves, 61 remain in effect as of February 2020, many in communities that are not even isolated
- oil sands, hydroelectric dams, diamond mines, and many other projects have negatively impacted Indigenous territories across Canada. Indigenous peoples have reaped very little of the economic benefits from these activities
- the remote geographic location of many Indigenous communities, in conjunction with complex jurisdictional issues, lead to debate over who is responsible for the health of these communities; this often leaves communities with delayed and inadequate responses to community needs
- Canada's adoption of the United Nations Declaration on the Rights of Indigenous Peoples (UNDRIP) will help rectify some of these detrimental activities on our environment and Indigenous peoples

Africville, Nova Scotia

- Halifax was founded in 1749
- African people, many of whom were descendants of slaves in Jamaica, dug out roads and built much of the city
- the early Black community lived a few kilometres north of the city in a community established on the Bedford Basin in Halifax, an area that became Africville
- the proximity to the waterfront for fishing, prospects for wage labour in the city, and establishment of structures including a post office, school, and church created a tight-knit Black community which, at one point, housed over 400 individuals and families
- facilities deemed otherwise unfit for surrounding areas were established in Africville by city council and businesses, including an oil plant, tar factory, prison, hospital for infectious diseases, and open garbage dump, with raw sewage and waste products emptying directly into the water supply
- the community was denied resources available to predominantly White neighbouring areas, despite being within the municipal jurisdiction, including garbage collection, law enforcement, paved roads, and appropriate water treatment
- in 1957, the city expropriated the land for industrial use and forced the relocation of residents, many of whom into public housing
- a settlement was reached between some former Africville residents and the City of Halifax in 2010, although an application for a class-action lawsuit submitted to the Supreme Court of Halifax was overturned in 2018
- on 24 February 2010, Halifax Regional Municipality Mayor Peter Kelly apologized for the destruction of Africville

Occupational Health

- a field involved in the prevention of illness or injury and the promotion of health in the work environment
- services encompass recognizing and controlling exposure to hazards (primary prevention), occupational health surveillance and screening (secondary prevention), and treatment and rehabilitation (tertiary prevention)
- occupational disease often looks clinically the same as non-occupational disease and, without a thorough occupational health history, may go unrecognized as distinct

Taking an Occupational Health History

- current and previous duties at place of employment
- exposures
  - identification: screen for chemical, metal, dust, biological, and physical hazards as well as psychological stressors - workers may bring safety data sheets (formerly MSDSs) that provide information about hazards of exposure
  - assessment: duration, concentration, route, exposure controls (e.g. ventilation and other environmental controls, personal protective equipment)
- temporal relationship: changes in symptoms in relationship to work environment, latency between first exposure and current symptoms
- presence of similar symptoms in co-workers
- non-work exposures to hazardous agents: home, neighbourhood, hobbies
- additional assessment may be required (e.g. chest radiography, ultrasound, pulmonary function tests)

Taking an Occupational Health Hx: WHACS

What do you do?
How do you do it?
Are you concerned about any particular exposures on or off the job?
Co-workers or others with similar problems?
Satisfied with your job?

Source: J Occup Environ Med 1998;40:680-684

Occupational Health Statistics

In 2018, 1027 workers died of work-related causes in Canada

The average time-loss injury rate between 2014-2018 ranged across Canadian provinces and territories from 1.02 to 2.89 per 100 workers

Provincial and territorial compensation boards do not cover all workplaces (e.g. most agricultural workers)

Compensation board insurance coverage ranges across provinces and territories from 74-99% of the workforce

Source: 2020 Report on Work Fatality and Injury Rates in Canada

Information about worker's compensation at: https://awcbc.org/en/

Occupational Hazards

Table 13. Occupational Hazards

Physical	Chemical	Biological	Psychosocial	Ergonomic/Safety
Noise (e.g. hearing loss) Temperature Heat cramps, heat exhaustion, heat stroke Hypothermia, frostbite Air pressure (e.g. barotrauma, decompression sickness) Radiation Non-ionizing: visible light, infrared Ionizing: UV, x-rays, γ rays Vibration-related disorders (e.g. secondary Raynaud's, whole body vibration)	Organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride) Mineral dusts (e.g. silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis) Heavy metals (e.g. nickel, cadmium, mercury, lead) Gases (e.g. halogen gases, sulphur dioxide, carbon monoxide, nitrogen oxides) Second-hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage) Skin diseases (major portion of compensations, e.g. contact dermatitis, occupational acne, pigmentation disorders)	Exposure to bacteria, viruses, fungi, protozoa, Rickettsia Exposure to biological proteins, endotoxins, enzymes, animal excreta Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B) Consider exposure to disease in endemic countries, travellers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. malaria, SARS, TB)	Workload stressors Responsibility Fear of job loss Geographical isolation Shift work Bullying Harassment (sexual/non-sexual) Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder) Workplace violence (involving staff, clients, the general public)	Workload stressors Responsibility Fear of job loss Geographical isolation Shift work Bullying Harassment (sexual/non-sexual) Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder) Workplace violence (involving staff, clients, the general public)

Workplace Legislation

- universal across Canada for corporate responsibility in the workplace: reasonable precautions to ensure a safe workplace, application of Workplace Hazardous Materials Information System (WHMIS), and existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally-regulated industries (e.g. airports, banks, highway transport) under the *Canada Labour Code*
- Ontario's *Occupational Health and Safety Act*
  - sets out rights of workers and duties of employers, procedures for workplace hazards, and law enforcement
  - workers have the right to:
    - know (e.g. be trained and have information about workplace hazards)
    - participate (e.g. have representatives on joint health and safety committees)
    - refuse work (e.g. workers can decline tasks they feel are overly dangerous)
    - note: for some occupations, this right is restricted if, for example, danger/risk is normal part of work or refusal would endanger others (e.g. police, firefighters, some health care workers)
    - stop work (e.g. 'certified' workers can halt work they feel is dangerous to other workers)
  - enforced by Ministry of Labour via inspectors
- *Health Protection and Promotion Act* (HPPA) (Ontario)
- Medical Officer of Health has right to investigate and manage health hazards where workplace exposures may impact non-workers (e.g. community members living close to the work site)

Workplace Health Promotion

- a strategy for addressing the health and well-being of workers in the workplace, not legislated
- may include education, event planning, information campaigns, and workplace supports to promote personal worker health and a healthy workforce

Workplace Primary Prevention

- proactive efforts to reduce workplace illness or injury
- achieved through anticipating, recognizing, evaluating, and controlling workplace hazards
- hierarchy of controls (see *Figure 18*) is followed to minimize exposure – elimination/substitution of hazards is most superior, followed by isolation (engineering controls), training and behavioural efforts (administrative controls), and lastly, personal protective equipment

Occupational Safety And Health Enforcement Tools For Preventing Occupational Diseases And Injuries
Cochrane DB Syst Rev 2013;8,CD010183
Purpose: To assess the effects of occupational safety and health regulation enforcement tools for preventing occupational diseases and injuries.
Outcome: Inspections decrease injuries in the long term, but not short term, with an unclear magnitude of effect.

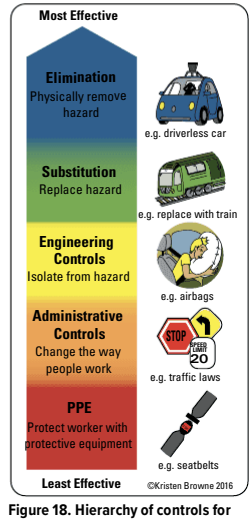

Figure 18. Hierarchy of controls for reduction of occupational exposures
Source: Modified from CDC. 2015. Hierarchy of controls. http://www.cdc.gov/niosh/topics/hierarchy/

***Ontario's Workplace Safety and Insurance Act* (each province will have their own corresponding legislation)**
- Establishes Workplace Safety and Insurance Board (WSIB), an autonomous government agency that oversees workplace safety training and administers insurance for workers and employers
- WSIB decides benefits for workers, which may include reimbursement for:
  - Loss of earned income
    - Non-economic loss (e.g. physical, functional, or psychological loss extending beyond the workplace)
    - Loss of retirement income
    - Health care expenses (e.g. first-aid, medical treatment)
    - Survivor benefits (e.g. dependents and spouses can receive benefits)
- Employers pay for costs (e.g. no government funding)
- No-fault insurance (e.g. worker has no right to sue the employer) in return for guaranteed compensation for accepted claims
- Negligence is not considered a factor
- Physicians are required to provide the WSIB with information about a worker's health without a medical waiver once a claim is made

For more information: http://www.wsib.on.ca/en/community/WSIB

Workplace Secondary Prevention

- for workers who are exposed to workplace hazards, goal is to identify earliest signs of overexposure or disease through medical surveillance (periodic examinations to identify early changes in a single worker or multiple workers). Some examples include:
  - whole blood lead testing to identify effectiveness of controls and to remove workers from exposure
  - pulmonary function tests for asthma (e.g. occupational dust exposure)
  - audiograms for hearing loss (e.g. occupational noise exposure)

Workplace Tertiary Prevention

- treatment of the disease or injury to facilitate safe and timely return to the workforce
- may require rehabilitation, retraining, change in job duties, and/or workers' compensation (WSIB)
- often also involves accommodating the workplace for a worker who has a non-occupational injury or illness, with routine reassessments of the fit between the worker and their duties - work that is considered safety-sensitive may be restricted for workers with ailments that could impede their ability to work safely, or a worker may be medically determined to have limitations with what they can reasonably do at work
- advise relevant authorities if necessary (e.g. report notifiable diseases to public health, conditions impeding driving to Ministry of Transportation)

Appendix – Mandatory Reporting

Reportable Diseases

As an essential part of the public health system, physicians in Canada are required by provincial law to report certain diseases to public health. Physician reporting is also outlined by provincial physician licensing Colleges (e.g. College of Physicians and Surgeons of Ontario (CPSO)). Failure to report can result in suspension of a license to practice.
The reasons that reporting is mandatory include:

1. to identify and control an outbreak
2. to prevent spread if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa Fever)
3. if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment, and/or partner notification (e.g. gonorrhea, TB)
5. surveillance (to monitor disease trends over time)

Diseases of Public Health Significance

Diseases marked with * (and Influenza in institutions) should be reported immediately to the Medical Officer of Health by either telephone or fax. Other diseases can be reported the next working day by fax, phone, or mail. Each province/territory has a similar legislation.

Acquired Immunodeficiency Syndrome (AIDS)
Acute flaccid paralysis <15 yr
Amoebiasis
Anthrax*

Botulism*
Brucellosis*
Blastomycosis

Campylobacter enteritis
Carbapenemase-Producing Enterobacteriaceae (CPE)
Chancroid
Chickenpox (Varicella)
Chlamydia trachomatis infections
Cholera*
*Clostridium difficile** associated disease (CDAD) outbreaks in public hospitals
Coronavirus novel including SARS, MERS, and COVID-19*
Creutzfeldt-Jakob Disease, all types*
Cryptosporidiosis*
Cyclosporiasis*
Diphtheria*

Echinococcus multilocularis infection
Encephalitis, including:
1. Primary, viral
2. Post-infectious
3. Vaccine-related
4. Subacute sclerosing panencephalitis
5. Unspecified

Food poisoning, all causes

Gastroenteritis, institutional outbreaks and in public hospitals*
Giardiasis, except asymptomatic cases*
Gonorrhea

Haemophilus influenzae b disease, all types*
Hantavirus pulmonary syndrome*
Hemorrhagic fevers*, including:
1. Ebola virus disease*
2. Marburg virus disease*
3. Other viral causes* (Lassa Fever*)
Hepatitis, viral*:
1. Hepatitis A*
2. Hepatitis B
3. Hepatitis C

Influenza (Note: Influenza in institutions*)

Legionellosis
Leprosy
Listeriosis
Lyme Disease

Measles*
Meningitis, acute*:
1. Bacterial*
2. Viral
3. Other
Meningococcal disease, invasive*
Mumps

Ophthalmia neonatorum

Paralytic shellfish poisoning
Paratyphoid fever
Pertussis (whooping cough)
Plague*
Pneumococcal disease, invasive
Poliomyelitis, acute*
Psittacosis/Ornithosis

Q Fever*

Rabies*
Respiratory infection outbreaks in institutions and public hospitals*
Rubella*
Rubella, congenital syndrome

Salmonellosis
Shigellosis*
Smallpox*
Syphilis

Tetanus
Trichinosis
Tuberculosis, active and latent Tularemia
Typhoid Fever

Verotoxin-producing E. coli infection* indicator conditions, including Hemolytic Uremic Syndrome (HUS)*

West Nile Virus illness, including:
1. West Nile fever
2. West Nile neurological manifestations

Yersiniosis

Other Reportable Conditions

- in addition to reporting diseases, physicians have a legal responsibility to report certain conditions. The list below highlights some reportable conditions for Ontario, but is not exhaustive. See your jurisdiction's regulatory body for the full list

Live Births, Stillbirths, and Deaths – to the Registrar General or Coroner*

- all live and stillbirths must be reported within 2 business days
- a physician with sufficient familiarity of a patient's illness or who was in attendance of a deceased patient's last illness must complete and sign the medical certificate of death
- physicians must contact a coroner or the police if patient is suspected to have deceased from violence, misadventure, negligence, misconduct or malpractice, or any cause other than disease; by unfair means; during pregnancy or postpartum from circumstances reasonably attributed to the pregnancy; suddenly and unexpectedly; from an illness not treated by a legally qualified medical practitioner; or under circumstances that may require investigation*
- physicians must report all medically assisted deaths to the coroner*

Child Abuse – to Local Children's Aid Society (CAS)

- all child abuse and neglect where reasonable grounds to suspect exist (including physical harm, emotional harm, sexual harm, and neglect)
- ongoing duty to report: if additional reasonable grounds are suspected, a further report to CAS is necessary

Gunshots Wounds – to Local Police Service

- all patients with gunshot or stab wounds should be reported as soon as is practical
- self-inflicted knife wounds are not reportable

Abuse of Long-Term Care or Retirement Home Residents – to the Registrar of the Retirement Homes Regulatory Authority or Long-Term Care Home Director

- any resident suspected of being subject to or at risk of improper or incompetent treatment or care, abuse or neglect, or unlawful conduct including financial abuse must be reported immediately

Unfit to Drive – to Provincial Ministry of Transportation

- all patients with a medical condition (e.g. dementia, untreated epilepsy, ophthalmological) that may impede their driving ability
- if a physician does not report and the driver gets into an accident, the physician may be held liable

Unfit to Fly – to Federal Ministry of Transportation

- all patients believed to be flight crew members or air traffic controller with a medical or optometric condition that is likely to constitute a hazard to aviation safety

Source: CPSO. Mandatory and Permissive Reporting. 2017. Available from: https://www.cpso.on.ca/Physicians/Policies-Guidance/Policies/Mandatory-and-Permissive-Reporting

Landmark Public Health and Preventive Medicine Trials

Trial Name	Reference	Clinical Trial Details
Mammography		
Swedish Two-County Trial	Radiology 2011;260(3):658-63	**Title**: Swedish Two-County Trial: Impact of Mammographic Screening On Breast Cancer Mortality During 3 Decades **Purpose**: Evaluate the long-term effect of mammographic screening on breast cancer mortality. **Methods**: 133065 women aged 40-74 yr were randomly assigned to either a group invited for mammographic screening or a control group. A negative binomial regression analyzed mortality. **Results**: At 29 yr of follow-up, a large significant reduction in breast cancer mortality was found in the group invited for mammographic screening compared to the control group (relative risk = 0.69; 95% CI: 0.56 to 0.84). **Conclusion**: Invitation to mammographic screening leads to a large significant decrease in breast cancer-related mortality.
MASS	BMJ 2009;338:b2307	**Title**: Primary outcomes were mortality and cost per life year gained over 10 years. **Results**: The invited group had 155 (0.46%) deaths related to AAA vs. 296 (0.87%) in the control group (RR 48%; 95% CI, 37%-57%). The cost effectiveness ratio was £7600 (£5100 to £13 000) per life year gained. **Conclusion**: Mortality benefit for men screened for abdominal aortic aneurysm by ultrasound is maintained for up to 10 years, with cost effectiveness increasing with time.
COLONPREV	NEJM 2012;366:697-706	**Title**: Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening **Purpose**: To compare the efficacy of colonoscopy and fecal immunochemical testing (FIT) on colorectal cancer (CRC) screening. **Methods**: RCT of adults aged 50-69 years who were asymptomatic and at average risk of CRC. Participants were randomized to receive a one-time colonoscopy or FIT q2 years. **Results**: Participation was 34.2% and 24.6% in the FIT and colonoscopy groups, respectively. CRC was detected in 0.1% of participants in both the colonoscopy and FIT groups (OR 0.99; 95% CI, 0.61-1.64; p = 0.99). Advanced adenomas were detected in 1.9% and 0.9% of participants in the colonoscopy and FIT groups, respectively (OR 2.30; 95% CI, 1.97-2.69; p<0.001). **Conclusion**: The incidence of colorectal cancer did not differ between subjects screened by colonoscopy as compared to FIT testing. More adenomas were detected in the colonoscopy group. Participation was higher in subjects undergoing FIT testing.

Trial Name	Reference	Clinical Trial Details
NLST	NEJM 2011;365:395-409	**Title**: Reduced Lung Cancer Mortality with Low-Dose Computed Tomographic Screening **Purpose**: To assess whether low-dose CT screening reduces lung cancer mortality. **Methods**: RCT of 53,454 patients at high risk of lung cancer who were randomly assigned to receive 3 annual low-dose CT scans or a single-view CXR. Primary outcomes were cases of lung cancer and lung cancer deaths. **Results**: Positive screening test rates were 24.2% and 6.9% in CT and radiography groups, respectively. Lung cancer incidence was 645 cases per 100,000 person years vs. 572 cases per 100,000 person years in CT and radiography groups, respectively (RR 1.13; 95% CI, 1.03-1.23). The relative reduction in mortality from lung cancer with low-dose CT screening was 20.0% as compared to radiography (95% CI, 6.8-26.7; p=0.004). **Conclusion**: Mortality from lung cancer is reduced with low-dose CT as a screening tool in high risk patient populations.
Vaccination		
VAXICOL	J Am Geriatr Soc 2009;57(9): 1580-6	**Title**: Effect of Influenza Vaccination of Nursing Home Staff on Mortality of Residents: A Cluster-Randomized Trial **Purpose**: Evaluate the impact of influenza vaccination among staff on all-cause mortality in nursing home residents. **Methods**: 40 nursing homes matched in pairs were randomly assigned to the vaccination arm or no-vaccination control arm. The vaccination arm involved a vaccine promotion campaign and administration program for staff. **Results**: Vaccination rates among staff in the vaccination arm were 69.9% compared to 31.8% in the no-vaccination arm. A strong correlation between staff vaccination coverage and all-cause mortality of the residents was found (correlation coefficient = -0.42, P=0.007). **Conclusion**: The results support staff of nursing homes being vaccinated against influenza to reduce all-cause mortality of residents.
NCT04368728	NEJM 2020;383:2603-2615	**Title**: Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine **Purpose**: To determine the safety and efficacy of the BNT162b2 mRNA covid-19 vaccine **Methods**: RCT of 43,548 participants aged 16 or older who were randomized to receive either the BNT162b2 mRNA vaccine or placebo. **Results**: Eight cases of Covid-19 occurred in the vaccine group as compared to 162 cases in the placebo group, indicating 95% efficacy of the vaccine in Covid-19 prevention (95% CI, 90.3-97.6). Serious adverse events were low and comparable between groups. **Conclusion**: The BNT162b2 mRNA Covid-19 vaccine provides 95% protection against Covid-19 in people aged 16 and older with comparable safety data to other viral vaccines at 2 months.

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R Respirology

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Differential Diagnoses of Common Presentations
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Airway Disease **R7**
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Asthma
Chronic Obstructive Pulmonary Disease
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Interstitial Lung Disease **R13**
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Known Etiologic Agents

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Pulmonary Vasculitis
Pulmonary Edema

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Mediastinitis
Pleural Effusions
Complicated Parapneumonic Effusion
Empyema
Atelectasis
Pneumothorax
Asbestos-Related Pleural Disease
Mesothelioma

Respiratory Failure **R27**
Hypoxemic Respiratory Failure
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Acronyms

A-a	alveolar-arterial gradient	CSA	central sleep apnea	LTRA	leukotriene receptor antagonist	PP	pulse pressure
ABG	arterial blood gas	CVP	central venous pressure	LA	left atrium	PPI	proton pump inhibitor
ACEi	angiotensin converting enzyme inhibitor	CWP	coal worker's pneumoconiosis	LV	left ventricle	PTT	partial thromboplastin time
AECOPD	acute exacerbation of COPD	DIC	disseminated intravascular coagulation	LVEDP	left ventricular end diastolic pressure	RA	rheumatoid arthritis
AHI	apnea hypopnea index	DLCO	Diffusing Lung Capacity for Carbon Monoxide	MEP	maximal expiratory pressure	RAD	right axis deviation
AIP	acute interstitial pneumonia	DOAC	direct oral anticoagulant	MIP	maximal inspiratory pressure	RAP	right atrial pressure
ALI	acute lung injury	DPD	distal phalangeal finger depth	MDI	metered dose inhaler	RF	rheumatoid factor
ALS	amyotrophic lateral sclerosis	DPI	dry powdered inhaler	MSK	musculoskeletal	RV	residual volume
ANA	antinuclear antibody	EBUS	endobronchial ultrasound	mMRC	modified medical research council dyspnea scale	RVEDV	right ventricular end diastolic volume
ANCA	anti-neutrophil cytoplasmic antibody	EGDT	early goal-directed therapy	NIPPV	noninvasive positive pressure ventilation	RVH	right ventricular hypertrophy
Anti-CCP	anti-cyclic citrullinated peptide antibody	ERV	expiratory reserve volume	NSIP	non-specific interstitial pneumonia	SABA	short-acting β2-agonists
aPTT	activated partial thromboplastin time	FEF	forced expiratory flow rate	N/V	nausea/vomiting	SAMA	short-acting muscarinic antagonist
ARDS	acute respiratory distress syndrome	FEV1	forced expiratory volume in 1 second	OSA	obstructive sleep apnea	SIRS	systemic inflammatory response syndrome
ASA	acetylsalicylic acid (Aspirin®)	FiO2	fraction of oxygen in inspired air	PA	posteroanterior	SOFA	sepsis-related organ failure assessment score
AV	arteriovenous	FRC	functional residual capacity	$PaCO_2$	arterial partial pressure of carbon dioxide	qSOFA	quick sepsis-related organ failure assessment score
BAPE	benign asbestos pleural effusion	FVC	forced vital capacity	PaO_2	arterial partial pressure of oxygen	SV	stroke volume
BG	blood glucose	GBM	glomerular basement membrane	PAO_2	alveolar partial pressure of oxygen	SVC	superior vena cava
BiPAP	bilevel positive airway pressure	GERD	gastroesophageal reflux disease	PAP	positive airway pressure	SVRI	systemic vascular resistance index
BSA	body surface area	H/A	headache	Patm	atmospheric pressure	TLC	total lung capacity
CA	cancer	HP	hypersensitivity pneumonitis	PCWP	pulmonary capillary wedge pressure	UC	ulcerative colitis
CAT	COPD assessment test	HPA	hypothalamic-pituitary axis	PE	pulmonary embolism	UIP	usual interstitial pneumonia
CCB	calcium channel blocker	IC	inspiratory capacity	PEEP	positive end expiratory pressure	URTI	upper respiratory tract infection
CF	cystic fibrosis	ICS	inhaled corticosteroid	PEF	peak expiratory flow	V/Q	ventilation-to-perfusion
CI	cardiac index	ILD	interstitial lung disease	PFT	pulmonary function tests	VC	vital capacity
CO	cardiac output	IPD	interphalangeal depth	PiO_2	inspired oxygen tension	VTE	venous thromboembolism
COP	cryptogenic organizing pneumonia	IPF	idiopathic pulmonary fibrosis			VT	tidal volume
CPAP	continuous positive airway pressure	LABA	long-acting β-agonist				
		LAMA	long-acting muscarinic antagonist				
		LMWH	low molecular weight heparin				

Approach to the Respiratory Patient

Basic Anatomy Review

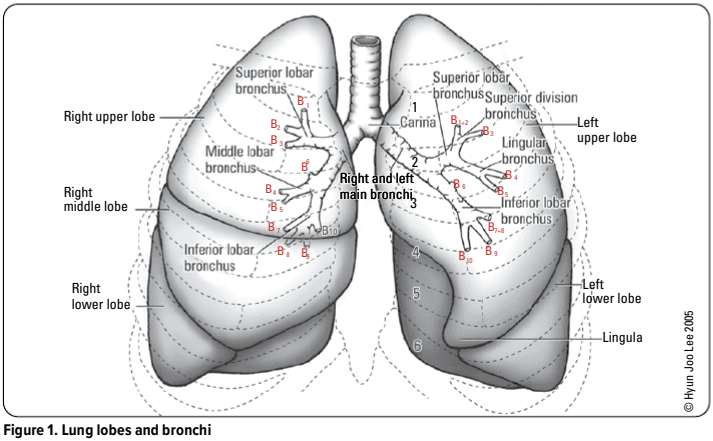


Figure 1. Lung lobes and bronchi

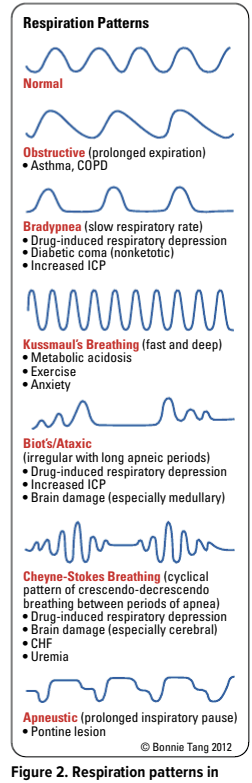


Figure 2. Respiration patterns in normal and disease states

Differential Diagnoses of Common Presentations

Table 1. Differential Diagnosis of Dyspnea

Acute Dyspnea (Minutes-Days)

Cardiac
- Acute Coronary Syndrome
- Acute Decompensated Heart Failure
- Acute myocardial infarction
- CHF exacerbation
- Cardiac tamponade
- Arrhythmia

Pulmonary
- Upper airway obstruction (anaphylaxis, aspiration, croup, EBV)
- Airway disease (asthma, COPD exacerbation, bronchitis)
- Parenchymal lung disease (ARDS, pneumonia)
- Pulmonary vascular disease (PE, vasculitis)
- Pleural disease (pneumothorax, tension pneumothorax, pleural effusion)

Neurologic/Psychogenic
- Respiratory control (metabolic acidosis, trauma)
- Anxiety
- Panic attack (Post Traumatic Stress Disorder)

Chronic Dyspnea (+4 Weeks)

Cardiac
- Valvular heart disease
- Myocardial dysfunction (decreased CO)

Pulmonary
- Airway disease (asthma, COPD)
- Parenchymal lung disease (interstitial disease)
- Pulmonary vascular disease (pulmonary HTN, vasculitis)
- Pleural disease (effusion)

Metabolic
- Medication
- Severe anemia
- Hyperthyroidism

Neuromuscular and chest wall disorders
- Deconditioning, obesity, pregnancy, neuromuscular disease

Psychogenic
- Anxiety

Table 2. Differential Diagnosis of Chest Pain

Nonpleuritic	Pleuritic
Pulmonary	**Pulmonary**
Neoplasm (rarely)	Pneumonia
Cardiac	PE
MI	Neoplasm
Myocarditis/pericarditis	Pneumothorax
Deconditioning	Pleurisy
Esophageal	Hemothorax
GERD	TB
Spasm	Empyema
Esophagitis	**Cardiac**
Ulceration	Pericarditis
Achalasia	Dressler's syndrome
Neoplasm	**GI**
Esophageal rupture	Subphrenic abscess
Mediastinal	**MSK**
Lymphoma	Costochondritis
Thymoma	Fractured rib/flail chest
Subdiaphragmatic	Myositis
Peptic ulcer disease	Herpes zoster
Gastritis	**Psychogenic**
Biliary colic	Anxiety
Pancreatitis	Panic attack/disorder
Vascular	
Aortic aneurysm	
Aortic dissection	
Aortic injury/rupture	
MSK	
Costochondritis	
Skin	
Breast	
Ribs	
Rheumatic disease	
Metabolic	
Anemia	
Hyperthyroidism	
Psych	
Anxiety	
Panic attack/disorder	
Miscellaneous	
Pregnancy	
Weight gain	

See Cardiology and Cardiac Surgery C5 and Emergency Medicine ER21

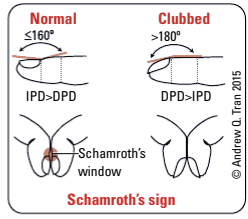


Figure 3. Signs of nail clubbing

Signs of Respiratory Distress
- Tachypnea
- Central/peripheral cyanosis
- Tachycardia
- Inability to speak
- Nasal flaring
- Tracheal tug
- Intercostal indrawing
- Tripoding
- Paradoxical breathing

Common Causes of Clubbing
Pulmonary: lung CA, bronchiectasis, pulmonary fibrosis, abscess, CF, TB, empyema, A-V fistula/malformation (NOT COPD)
Cardiac: cyanotic congenital heart disease, endocarditis
GI: inflammatory bowel disease, celiac, liver cirrhosis, neoplasm
Endocrine: Graves' disease
Other: other malignancy, primary hypertrophic osteoarthropathy

Clubbing is not seen in COPD – if present, think malignancy

Hemoptysis

Most common cause is bronchitis

90% of massive hemoptysis is from the bronchial arteries

Definitions for hemoptysis vary, often defined as "massive" if >600 mL/24 h or bleeding rate of >100 mL/h

Most Common Causes of Chronic Cough in the Non-smoking Patient (Cough >3 mo with Normal CXR)

GERD

Asthma

Postnasal drip

ACEI

Table 3. Differential Diagnosis of Hemoptysis

Hemoptysis DDx

Airway Disease
- **Acute or chronic bronchitis***
- Bronchiectasis and CF
- Bronchogenic CA
- Bronchial carcinoid tumour

Parenchymal Disease
- Pneumonia
- TB
- Lung abscess
- Fungal infection
- Primary lung cancer
- Pulmonary metastasis

Vascular Disease
- PE
- Elevated pulmonary venous pressure:
  - Left ventricular dysfunction/failure
  - Mitral stenosis
- Vascular malformation
- Vasculitis:
- ANCA related vasculitides
  - Goodpasture's syndrome
  - Idiopathic pulmonary hemosiderosis

Miscellaneous
- Iatrogenic (lung biopsy, airway ablation procedures)
- Impaired coagulation
- Pulmonary endometriosis – catamenial hemoptysis
- Trauma
- Foreign body

*Most common cause of hemoptysis

Table 4. Differential Diagnosis of Cough

Cough DDx

Airway Irritants
- Inhaled smoke, dusts, fumes
- Postnasal drip (upper airway cough syndrome)
- Aspiration

Gastric contents (GERD)*
- Laryngopharyngeal reflux
- Oral secretions
- Foreign body

Airway Disease

URTI including postnasal drip and sinusitis*
- Acute or chronic bronchitis
- Bronchiectasis
- Neoplasm
- External compression by node or mass lesion

Asthma*
- COPD

Parenchymal Disease
- Pneumonia
- Lung abscess
- Interstitial lung disease

PE

CHF

Drug-induced (e.g. ACEI)

Smoking

*"Big Three" causes of chronic cough

Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008. With permission from Elsevier

Pulmonary Function Tests

- useful in differentiating the pattern of lung disease (obstructive vs. restrictive)
- assess lung volumes, flow rates, and diffusion capacity
- note: normal values for FEV_1 are interpreted by comparing to the predicted upper and lower limits of normal (for age, sex, and height); "Race" differences in predicted values are recognized but are not fully understood and likely represent genetic ancestry and the effects of the social determinants of health

Table 5. Comparison of Lung Flow and Volume Parameters in Lung Disease

	Obstructive	Restrictive
	Decreased flow rates (most marked during expiration)	Decreased lung compliance
	Air trapping (increased RV/TLC)	Decreased lung volumes
	Hyperinflation (increased TLC)	
DDx	Asthma, COPD, bronchiolitis, bronchiectasis/CF*	ILD, pleural disease, neuromuscular disease, chest wall disease
FEV_1/FVC	Reduced	Elevated or normal
TLC	Elevated or normal	Reduced
RV	Elevated or normal	Reduced, normal or elevated
RV/TLC	Elevated or normal	Normal or elevated (neuromuscular disease may have elevated RV/TLC ratio)
DLCO	Normal or reduced depending on disease state	Reduced or normal depending on whether parenchymal or extraparenchymal restriction is present

*Bronchiectasis can be obstructive or mixed

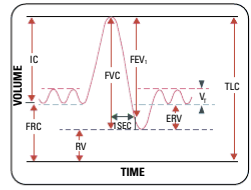


Figure 4A. Lung volumes and capacities

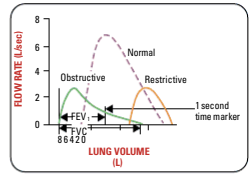


Figure 4B. Expiratory flow volume curves

Adapted with permission from Elsevier. Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008

Table 6. Common Respirology Procedures

Technique	Purpose	Description
Plethysmography ("body box")	Measure FRC	After a normal expiration, the patient inhales against a closed mouthpiece Resultant changes in the volume and pressure of the plethysmograph are used to calculate the volume of gas in the thorax Useful for patients with air trapping
He Dilution	Measure FRC	A patient breathes from a closed circuit containing a known concentration and volume of helium Since the amount of helium remains constant, FRC is determined based on the final concentration of the helium in the closed system Only includes airspaces that communicate with the bronchial tree and is dependent on airflow – may underestimate volumes in patients with gas trapping
Bronchoscopy	Diagnosis and therapy	A flexible or rigid bronchoscope is used for visualization of a patient's airways allows for: Bronchial and broncho-alveolar lavage (washings) for culture, cell count analysis, and cytology Endobronchial or transbronchial tissue biopsies Removal of secretions/foreign bodies/blood Laser resections Airway stenting Mediastinal lymph nodes can also be sampled using a special bronchoscope equipped with an U/S probe (EBUS)

Lung Volumes

ERV – Expiratory Reserve Volume
FEF – Forced Expiratory Flow Rate
FEV_1 – Forced Expiratory Volume (in one second)
FRC – Functional Residual Capacity
IC – Inspiratory Capacity
RV – Residual Volume
TLC – Total Lung Capacity
FVC – Forced Vital Capacity
VT – Tidal Volume

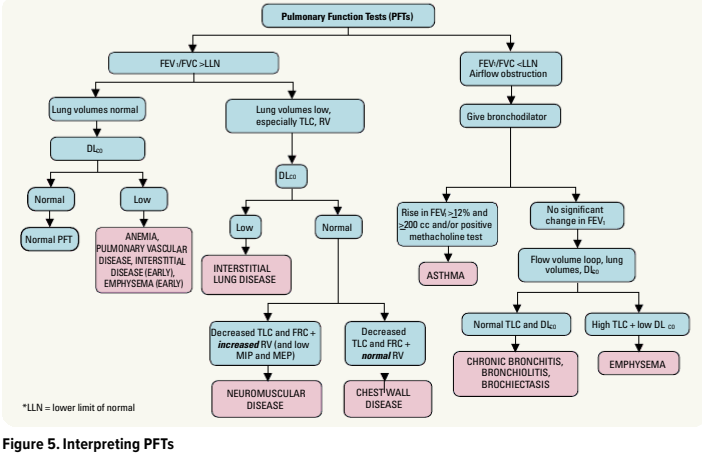


Figure 5. Interpreting PFTs

Chest X-Rays

- see Medical Imaging, MI4

Table 7. CXR Patterns and Differential Diagnosis

Pattern	Signs	Common DDx
Consolidation ("Airspace disease")	Air bronchogram Silhouette sign Less visible blood vessels	Acute: water (CHF), pus (pneumonia), blood (hemorrhage) Chronic: neoplasm (lymphoma, bronchioloalveolar carcinoma), inflammatory (eosinophilic pneumonia, organizing pneumonia), infection (TB, fungal)
Reticular ("Interstitial disease")	Increased linear markings Fine or ground glass opacities Honeycombing (clustered cystic changes seen in IPF usually, but also in rheumatoid arthritis, asbestosis etc.)	ILD (IPF, collagen vascular disease, asbestos, drugs, HP)
Nodular	Cavitary vs. non-cavitary	Cavitary: neoplasm (primary – squamous cell carcinoma vs. metastatic cancer), infectious (anaerobic or Gram negative, TB, fungal), inflammatory (RA, sarcoidosis, granulomatosis with polyangiitis (GPA)) Non-cavitary: above + sarcoidosis, Kaposi's sarcoma (in HIV), silicosis, and coal worker's pneumoconiosis

Arterial Blood Gases

- provides information on acid-base and oxygenation status
- see Nephrology, NP17

Approach to Acid-Base Status

1. Is the pH acidemic (pH <7.35), alkalemic (pH >7.45), or normal (pH 7.35-7.45)?
2. What is the primary disturbance?
   metabolic: change in HCO_3^- and pH in same directions
   respiratory: change in HCO_3^- and pH in opposite directions
3. Is there appropriate compensation? (see *Table 8*)
   metabolic compensation occurs over 2-3 d reflecting altered renal HCO_3^- production and excretion
   respiratory compensation through ventilatory control of $PaCO_2$ occurs immediately
   inadequate compensation may indicate a second acid-base disorder

Table 8. Expected Compensation for Specific Acid-Base Disorders

Disturbance	$PaCO_2$ (mmHg) (normal ~40)	HCO_3^- (mmHg) (normal ~24)
Respiratory Acidosis		
Acute	↑ 10	↑ 1
Chronic	↑ 10	↑ 3
Respiratory Alkalosis		
Acute	↓ 10	↓ 2
Chronic	↓ 10	↓ 5
Metabolic Acidosis	↓ 1	↓ 1
Metabolic Alkalosis	↑ 5-7	↑ 10

4. If the patient has metabolic acidosis, what is the anion gap and osmolar gap?
   - anion gap = $[Na^+]-([Cl^-]+[HCO_3^-])$; normal 5-14 mmol/L
   - osmolar gap = measured osmolarity – calculated osmolarity = measured – (2[Na^+] + glucose + urea); normal ≤10 mmol/L
   - abnormal osmolar gap indicates the presence of alcohols
5. If anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
   - if not, consider a mixed metabolic picture

Table 9. Differential Diagnosis of Respiratory Acidosis

Increased P_aCO_2 secondary to hypoventilation

Respiratory Centre Depression (Decreased RR)	Neuromuscular Disorders (Decreased Vital Capacity)	Lung Disease	Mechanical Hypoventilation (Inadequate Mechanical Ventilation)
Drugs (anesthesia, sedatives, narcotics) Trauma Encephalitis Stroke Central apnea Supplemental O_2 in chronic CO_2 retainers (e.g. COPD)	Myasthenia gravis Guillain-Barré syndrome Botulism Poliomyelitis Muscular dystrophies ALS Myopathies Chest wall disease (obesity, kyphoscoliosis)	Chronic: COPD, CF Acute: Asthma Pulmonary edema Pneumothorax Pneumonia ILD (late stage) ARDS	

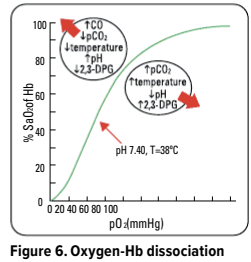


Figure 6. Oxygen-Hb dissociation curve

Factors that Shift the Oxygen-Hb Dissociation Curve to the Right

"CADET, face right!"
CO_2
Acid
2,3-DPG
Exercise
Temperature (increased)

Note: 2,3-DPG (2,3-diphosphoglycerate) is now called 2,3-BPG (2,3-bisphosphoglycerate)

Acidosis ↔ Hyperkalemia
Alkalosis ↔ Hypokalemia

Note: Mixed acid-base disturbances can still have a "normal" pH

Osmolar Gap = measured osmolarity – calculated osmolarity; for calculated osmolarity think "2 salts and a sticky BUN" (2Na + glucose + urea)

Table 10. Differential Diagnosis of Respiratory Alkalosis

Decreased $PaCO_2$ secondary to hyperventilation

Systemic Diseases	Respiratory Centre Stimulation	Mechanical Hyperventilation (Excessive Mechanical Ventilation)
Pulmonary disease (pneumonia, edema, PE, interstitial fibrosis)	Drugs (ASA, progesterone, theophylline, catecholamines, psychotropics, nicotine, salicylates)	
Severe anemia	Hepatic failure	
Heart failure	Gram-negative sepsis	
	Pregnancy	
	Anxiety	
	Pain	
	High altitude	

- see Nephrology, NP19 for differential diagnosis of metabolic acidosis and alkalosis

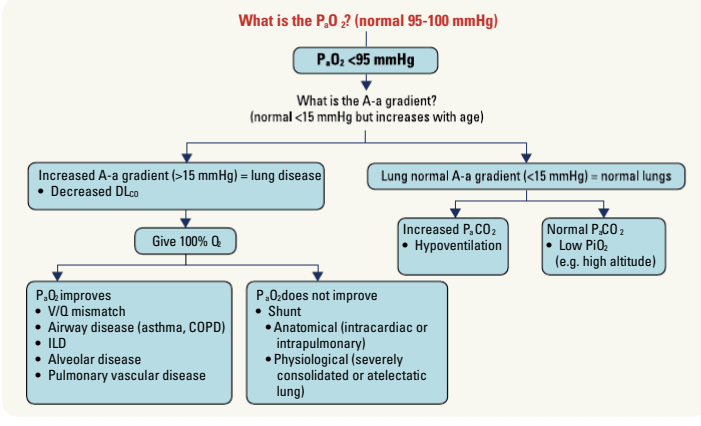


Figure 7. Approach to hypoxemia
*Note: In pediatric patients, normal A-a gradient is <15 mmHg (~5-10 mmHg)

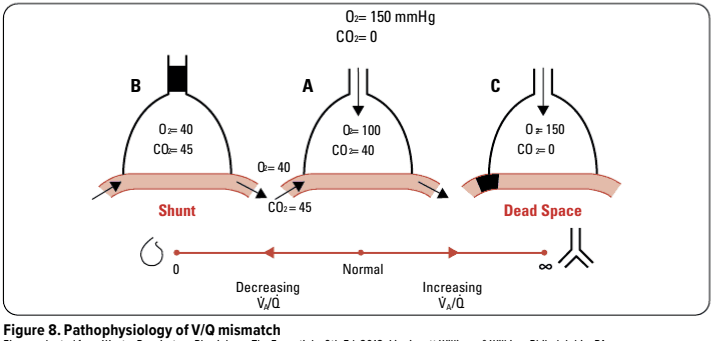


Figure 8. Pathophysiology of V/Q mismatch
Figure adapted from West – Respiratory Physiology: The Essentials. 9th Ed. 2012. Lippincott Williams & Wilkins, Philadelphia, PA

Anion Gap Metabolic Acidosis

MUDPILESCAT
Methanol
Uremia
Diabetic ketoacidosis/starvation ketoacidosis
Phenformin/Paraldehyde
Isoniazid, Iron, Ibuprofen
Lactic acidosis
Ethylene glycol
Salicylates
Cyanide, Carbon dioxide
Alcoholic ketoacidosis
Toluene, Theophylline

At Sea Level on Room Air
FiO_2 = 0.21
P_{atm} = 760 mmHg
PH_2O = 47 mmHg
RQ = 0.8
Thus, A-aDO_2 gradient on room air
A-aDO_2 = (150 – 1.25 [PaO_2]) – PaO_2
PiO_2 = (FiO_2 x (barometric pressure – PH_2O))

Diffusion Capacity for CO

DL_{CO} decreases in:
- ILD
- Pulmonary vascular disease
- Anemia
- Emphysema (decreased surface area)

DL_{CO} increases in/with:
- Asthma
- Obesity
- Pulmonary hemorrhage
- Left-to-right intracardiac shunt
- Polycythemia
- Post-exercise physiology (increased pulmonary blood volume)

Pulmonary Shunt
When blood bypasses the alveolar membrane by means of an abnormal circulation pathway and reaches the pulmonary venous system with de-oxygenated hemoglobin.
Shunt-like physiology occurs when blood passes through areas of the lung that have very little ventilation (e.g. densely consolidated lung in a severe pneumonia)

Airway Disease

Pneumonia

- see Pediatrics, P68

Asthma

- see Family Medicine, FM19 and Pediatrics, P91

Definition
- chronic inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
- associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli
- inflamed airways undergo a variety of changes including hypertrophy of airway smooth muscle and hyperplasia of mucous-producing goblet cells

Epidemiology
- common, 10.8% of Canadians (3.8 million); 8-10% of adults, 10-15% of children (however often misdiagnosed because inaccurate clinical diagnosis, failure to use objective testing)
- most children with asthma significantly improve in adolescence
- often family history of atopy (asthma, allergic rhinitis, eczema)
- work-related asthma (includes work-exacerbated asthma, or occupational asthma caused by high or low molecular weight sensitizer exposure)

Pathophysiology
Severe asthma attack:
- airway obstruction → V/Q mismatch → hypoxemia → ↑ventilation → ↓$PaCO_2$ → ↑pH and muscle fatigue → ↓ventilation, ↑$PaCO_2$/↓pH

Signs and Symptoms
- dyspnea, wheezing, chest tightness, cough, sputum
- symptoms usually occur or worsen at night or early morning
- symptoms can be paroxysmal or persistent
- when having an asthma attack: signs of respiratory distress, pulsus paradoxus

Table 11. Criteria for Determining if Asthma is Well Controlled

Daytime symptoms ≤2 d/wk	No asthma-related absence from work/school
Night-time symptoms <1 night/wk	β2-agonist use ≤2 times/wk
Physical activity normal (unimpaired by symptoms)	FEV_1 or PEF ≥90% of personal best
Exacerbations mild, infrequent (no ER visit, hospitalization, use of prednisone)	PEF diurnal variation <10-15%

Can J Respir Crit Care Sleep Med 2021; 5:6, 348-361

Table 12. Pulmonary Function Criteria for Diagnosis of Asthma (in ages 6+)

Preferred Measurement	Alternative Measurements
Spirometry Showing Reversible Airway Obstruction 1. ↓ FEV_1/FVC below lower limit of normal Adults: typically <0.75 to 0.8 Children age 6+: typically <0.8-0.9 AND 2. ↑ FEV_1 ≥12% (and ≥200 mL in adults) after bronchodilator or a course of controller therapy	**Peak Expiratory Flow Variability** 1. ↑ in PEF after a bronchodilator or course of controller therapy Adults: PEF increase ≥60 L/min (and ≥20%) OR Diurnal variation >8% for twice daily readings (>20% for multiple daily readings) Children age 6+: PEF increase ≥20% **Positive Challenge Test** 1. Methacholine challenge: positive if FEV_1 ↓ ≥20% at any inhaled methacholine dose <4 mg/mL (borderline if 4-16 mg/mL is required) 2. Post-exercise: ↓ FEV_1 ≥10-15%

Adapted from: Can J Respir Crit Care Sleep Med 2021; 5:6, 348-361

Treatment
- environment: identify and avoid triggers
- patient education: features of the disease, goals of treatment, self-management asthma action plan, inhaler technique
- pharmacological
  - symptomatic relief in acute episodes: short-acting β2-agonist or combined, long acting β2-agonist with inhaled corticosteroid (formoterol/budesonide)

Red Flags
Severe tachypnea/tachycardia, respiratory muscle fatigue, diminished expiratory effort, cyanosis, silent chest, decreased LOC

Central cyanosis is not detectable until SaO_2 is <85%. It is more easily detected in polycythemia and less readily detectable in anemia

Asthma Triggers
Irritants, such as:
- URTIs
- Emotion/anxiety
- Cold air
- Exercise
- GERD
- Cigarette smoke, air pollution
- Strong scents

Allergens, such as:
- Pet dander
- House dust
- Mould
- Cockroaches
- Seasonal allergens (grass/tree/weed/ragweed)

Other:
- NSAIDs (Samter's triad = asthma, NSAID sensitivity, nasal polyps)
- β-blockers (especially non-cardioselective)
- Hormonal fluctuations

Remember to step down therapy to lowest doses which maintain good asthma control, as patient improves

Airway Obstruction (Decreased FEV_1)
- Asthma
- COPD (chronic bronchitis, emphysema)
- Bronchiectasis (obstructive or mixed)
- Cystic fibrosis (obstructive or mixed)

Signs of Poor Asthma Control

"DANGERS"
Daytime Sx ≥3 d/wk
Activities (physical) reduced
Night-time Sx ≥1 night/wk
GP visits (unscheduled visits for exacerbations, requiring steroids)
ER visits or hospitalizations for exacerbations
Rescue puffer (SABA) use ≥3 times/wk
School or work absences

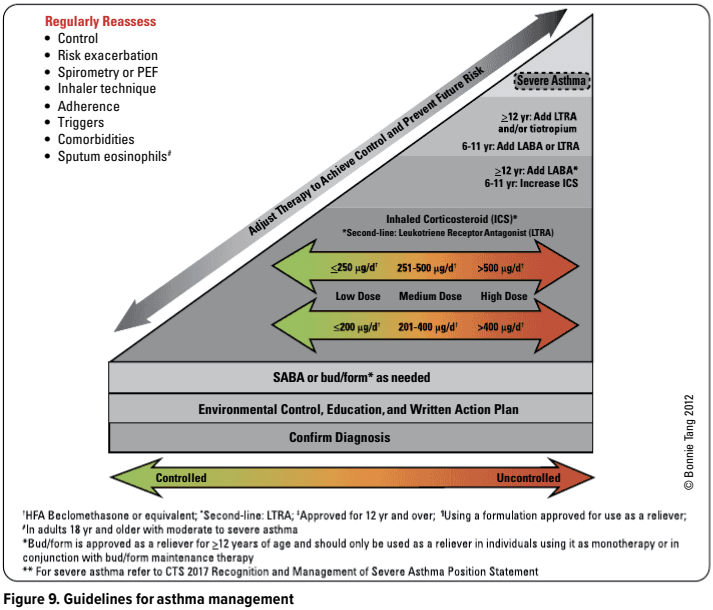
- long-term maintenance: any patient with poor control (*Table 11, R7*) and/or at risk of exacerbations should be on an inhaled corticosteroid-containing regimen (see *Figure 9*)
- risk of exacerbation defined as any of: 1) history of a previous requiring any of: systemic steroids, ED visit or hospitalization, 2) poorly-controlled asthma, 3) overuse of SABA (defined as use of more than 2 inhalers of SABA in 1 year), or 4) current smoker
  1. start with daily inhaled corticosteroids (or long acting β2-agonist with inhaled corticosteroid (formoterol/budesonide) as needed in patients ≥ 12 y/o – especially in patients expected to have low adherence to a daily inhaled corticosteroid)
  2. add long-acting β2-agonists to low dose inhaled corticosteroids in adults (use a combination inhaler; avoid separate ICS and LABA inhalers)
  3. escalate inhaled corticosteroid dose
  4. consider LTRA, long-acting anticholinergics, oral corticosteroids, and biologics (e.g. anti-IgE agents, including omalizumab, anti-IL5/IL5R agents, such as mepolizumab, and anti-IL-4/13 drugs, including dupilumab)

Emergency Management of Asthma

- see Emergency Medicine, ER29

1. inhaled β2-agonist first line (MDI route and spacer device recommended)
2. systemic steroids (PO or IV if severe)
3. if severe, add anticholinergic therapy ± magnesium sulfate
4. SC/IV adrenaline if caused by anaphylaxis or if unresponsive to inhaled β2-agonist
5. rapid sequence intubation in life-threatening cases (plus 100% O_2, monitors, IV access)
6. inhaled corticosteroid maintenance therapy at discharge

Guidelines for Asthma Management



†HFA Beclomethasone or equivalent; ‡Second-line: LTRA; #Approved for 12 yr and over; †Using a formulation approved for use as a reliever; #In adults 18 yr and older with moderate to severe asthma
*Bud/form is approved as a reliever for ≥12 years of age and should only be used as a reliever in individuals using it as monotherapy or in conjunction with bud/form maintenance therapy
** For severe asthma refer to CTS 2017 Recognition and Management of Severe Asthma Position Statement

Figure 9. Guidelines for asthma management
Adapted from: Can J Respir Crit Care Sleep Med 2021; 5:6, 348-361

Chronic Obstructive Pulmonary Disease

- see Family Medicine, FM19

Definition

- progressive and irreversible condition of the lung characterized by chronic obstruction to airflow with many patients having periodic exacerbations, gas trapping, lung hyperinflation, and at end stages, weight loss
- spirometry required for diagnosis (post-bronchodilator FEV_1/FVC <0.70 or lower limit of normal) (also often "overdiagnosed" due to inaccuracy of a clinical diagnosis)
- 2 phenotypes: chronic bronchitis and emphysema (usually coexist to variable degrees)
- gradual decrease in FEV_1 over time, more rapidly with each acute exacerbation

Asthma Action Plan
A written plan developed by providers for patients with asthma, which includes signs and symptoms for patients to recognize acute loss of asthma control (typically denoted as 'green' for good control, 'yellow' for transient loss of control, or 'red/emergency' zones) and personalized treatment instructions for each zone (usually quadrupling inhaled corticosteroid dose in the yellow zone for 7-14 d)

Addition of Long-Acting β2-Agonists to Inhaled Corticosteroids vs. Same Dose Inhaled Corticosteroids for Chronic Asthma in Adults and Children
Cochrane DB Syst Rev 2010;CD005535
Purpose: To quantify the safety and efficacy of addition of LABAs to ICS in asthmatic patients insufficiently controlled on ICS alone.
Methods: RCTs comparing addition of inhaled LABAs vs. placebo to the same dose of ICS in children 2 yr and above and in adults were included.
Results: 77 studies, 16623 adults and 4625 children. Addition of a daily LABA to ICS reduced risk of exacerbations requiring oral steroids by 23% and led to a significantly greater improvement in FEV_1 compared to ICS monotherapy.
Conclusions: In adults who are symptomatic on low to high doses of ICS monotherapy, the addition of a LABA reduces rate of exacerbations and improves lung function. In children, the effects of this treatment are uncertain.

Add a LABA to ICS for patients with any criteria for poorly controlled asthma

ICS-Formoterol Reliever vs. ICS and SABA Reliever in Asthma: a Systematic Review and Meta-Analysis
ERJ Open Research 2020;7
Purpose: Conduct a systematic review and meta-analysis to evaluate the efficacy of as needed ICS-formoterol versus ICS + as needed SABA in patients with mild-moderate asthma.
Methods: RCTs comparing as needed ICS-formoterol versus ICS + as needed SABA in adults and/or children with mild-moderate asthma were included, excluding studies that did not report severe exacerbations. Databases searched were EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. The primary study outcome was time to first exacerbation.
Results: After applying eligibility criteria, 4 RCTs were included in the meta-analysis, all comparing budesonide DPI budesonide + as needed SABA to DPI budesonide-formoterol. Budesonide-formoterol as needed reduced the rate ratio and odds of primary outcome (RR 0.85, 95% CI 0.73 to 1.00; OR 0.86; 95% CI 0.73 to 1.01).
Conclusion: There was a modest 15% reduction in the hazard ratio of first exacerbation with budesonide formoterol as needed combination versus the ICS + as needed SABA maintenance regimen. Currently, there remains no agreed standard for a minimal clinically important difference. Overall, this study is consistent with the GINA 2021 recommendations preferring ICS-formoterol as-needed over ICS maintenance therapy in mild asthma. Note that Canadian guidelines still recommend ICS + as needed SABA as first line for patients with suboptimal control, as it may be superior to budesonide-formoterol as needed combination for symptom control, and considers them equal alternatives for those who have good symptom control but are otherwise at high risk for exacerbations. A decision aid is available to assist patients/providers when selecting between these options (www.asthmadecisionaid.com).

Table 13. Clinical and Pathologic Features of COPD*

Chronic Bronchitis	Emphysema
Defined Clinically	**Defined Pathologically**
Productive cough on most days for at least 3 consecutive mo in 2 successive yr Obstruction is mostly due to narrowing of the airway lumen by mucosal thickening and excess mucus Airway changes include increased goblet cells, fibrosis of bronchioles, loss of tethering due to destruction of alveolar walls	Dilation and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse (obstruction), and air trapping
	2 Types 1. Centrilobular (respiratory bronchioles predominantly affected) Typical form seen in smokers, primarily affects upper lung zones 2. Panacinar (all parts of acinus) Accounts for about 1% of emphysema cases, typically from α1-antitrypsin deficiency, primarily affects lower lobes

*Note that the pathological changes of chronic bronchitis and emphysema can exist without obstruction. Only if spirometric obstruction is also present is it termed COPD

Risk Factors

- smoking is the #1 risk factor in Western countries
- environmental: exposure to wood smoke or other biomass fuel for cooking (especially in developing countries), air pollution, occupational exposures
- treatable factors: α1-antitrypsin deficiency, HIV (accelerated COPD progression), concurrent bronchial hyperactivity (asthma-COPD overlap – "ACO")
- demographic factors: age, history of childhood respiratory infections, low socioeconomic status

Signs and Symptoms

Table 14. Clinical Features and Investigations for Emphysema and Chronic Bronchitis

	Symptoms	Signs	Investigations
Chronic Bronchitis (Blue Bloater*)	Chronic productive cough Purulent sputum	Cyanosis (2° to hypoxemia) Peripheral edema from RHF (cor pulmonale) Crackles, wheezes Prolonged expiration Frequently obese	**PFT:** ↓ FEV_1, ↓ FEV_1/FVC N TLC, ↓ or N DL_{CO} **CXR:** AP diameter normal ↑ bronchovascular markings Enlarged heart with cor pulmonale (end-stage)
Emphysema (Pink Puffer*)	Dyspnea (± exertion) Minimal cough Tachypnea Decreased exercise tolerance	Pink skin Pursed-lip breathing Accessory muscle use Cachectic appearance due to energy consumption from increased work of breathing Hyperinflation/barrel chest Hyperresonant percussion Decreased breath sounds Decreased diaphragmatic excursion	**PFT:** ↓ FEV_1, ↓ FEV_1/FVC ↑ TLC (hyperinflation) ↑ RV (gas trapping) ↓ DL_{CO} **CXR:** ↑ AP diameter Flat hemidiaphragm (on lateral CXR) ↓ cardiac silhouette size ↑ retrosternal space Bullae ↓ peripheral vascular markings

*Note that "blue bloater" and "pink puffer" phenotypes are extremes and most COPD patients have elements of both. They are also outdated terms rarely used in clinical practice.

Natural Progression of COPD

40s Chronic productive cough, wheezing occasionally
50s 1st acute chest illness
60s Dyspnea on exertion, increasing sputum, more frequent exacerbations
Late Stage Hypoxemia with cyanosis, polycythemia, hypercapnia (morning headache), cor pulmonale, weight loss

Complications of COPD

Chronic hypoxemia
Polycythemia 2° to hypoxemia
Pulmonary HTN from loss of vascular bed (emphysema)
Cor pulmonale
Pneumothorax due to rupture of emphysematous bullae
Depression
COPD exacerbations

CO_2 Retainers

On ABG, retainers have chronically elevated CO_2 levels, usually with a near normal pH (due to metabolic compensation). Maintain O_2 saturation between 88-92% to prevent exacerbating hypercapnia due to worsening V/Q mismatch, Haldane effect, and/or decreased respiratory drive (in order of physiologic importance)

Remember, the most important intervention for COPD patients who smoke is smoking cessation

Table 15. Treatment of Stable COPD

Treatment	Details
Prolong Survival	
Smoking Cessation	Counselling, nicotine replacement (long + short-acting), bupropion, varenicline, combinations thereof
Vaccination	Annual influenza vaccination; pneumococcal vaccination
Home Oxygen	Prevents cor pulmonale and decreases mortality if used >15 h/d; indicated if: (1) PaO_2 ≤55 mmHg or (2) PaO_2 56-59 mmHg with cor pulmonale or polycythemia
LAMA/LABA/ICS triple Therapy	Mortality benefit in COPD patients at a high risk of exacerbations, with a high symptom burden and/or health status impairment (CAT score ≥10 and/or mMRC score ≥2) and FEV $_1$ <80% predicted
Symptomatic Relief and Exacerbation Prevention	
Inhaled bronchodilators (mainstay of therapy for most patients, used in combination)	Short-acting bronchodilators: recommended in all patients for prn relief of dyspnea
	SABAs (e.g. salbutamol, terbutaline): rapid onset
	SAMAs (e.g. ipratropium bromide): slightly more effective than SABAs with fewer side effects but slower onset
	Combination therapy SABA/SAMA can be used
	Long-acting bronchodilators: reduce dyspnea, improve exercise tolerance, and health status, reduce exacerbations. Recommended for any patient with dyspnea (mMRC ≥1)
	LABAs (e.g. salmeterol, formoterol, indacaterol)
	LAMAs (e.g. tiotropium bromide, glycopyrronium bromide): greater effect at improving dyspnea, exercise intolerance, and health status compared to LABAs
	LABA/LAMA dual therapy is recommended in patients with moderate to high symptom burden/health status impairment (CAT ≥10 and mMRC ≥2) and FEV1 <80% predicted
	LABA/LAMA/ICS triple therapy should be used in patients with low exacerbation risk but high symptom burden and/or health status impairment (CAT ≥10 and/or mMRC ≥2) and impaired lung function (FEV$_1$ <80% predicted) despite LAMA/LABA dual therapy or ICS/LABA combination therapy, and in any patient who meets criteria for mortality benefit (as above)
Inhaled Corticosteroids (ICS)	ICS monotherapy has been shown to increase the incidence of pneumonia in COPD; ICS should only be used as part of a combination inhaler with LABA or with LABA/LAMA as triple therapy, as per criteria above, and/or for concomitant asthma
Oral Therapies	Macrolide therapy reduces exacerbations and is recommended in patients with a high risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥10 and/or mMRC ≥2) and FEV$_1$<80% predicted who continue to exacerbate despite being on LAMA/LABA/ICS triple combination therapy
	PDE4 inhibitor therapy [roflumilast (Daxas®)] reduces exacerbations and is recommended in patients with a Chronic Bronchitic Phenotype at a high risk of exacerbations, with a high symptom burden and/or health status impairment (CAT ≥10 and/or mMRC ≥2) and FEV $_1$ <80% predicted who continue to exacerbate despite being on LAMA/LABA/ICS triple combination therapy
	N-Acetyl Cysteine (NAC) reduces exacerbations and is recommended in patients with a Chronic Bronchitic Phenotype at a high risk of exacerbations, with a high symptom burden and/or health status impairment (CAT ≥10 and/or mMRC ≥2) and FEV$_1$ <80% predicted who continue to exacerbate despite being on LAMA/LABA/ICS triple combination therapy
	There is insufficient or equivocal evidence to determine whether the addition of oral theophylline confers benefit in stable COPD (high-risk toxicity profile: nervous tremor, nausea/vomiting/diarrhea, tachycardia, arrhythmias, sleep changes)
	Oral corticosteroids: used to treat acute exacerbations; patients should be warned of side effects
Surgical	Lung volume reduction surgery (resection of emphysematous parts of lung in select patients, avoided due to higher mortality if FEV $_1$ <20%)
	Lung transplant
Other	Patient education, vaccination, oxygen if required, eliminate respiratory irritants/allergens (occupational/environmental)
	Pulmonary rehabilitation: may reduce mortality if offered within 2 wk after hospitalization with an acute exacerbation of COPD; should be offered to any patient with high symptom burden and/or frequent exacerbations to improve symptoms, quality of life, physical endurance and to reduce exacerbations

*High risk of exacerbations: ≥2 moderate acute exacerbations of COPD or ≥1 severe acute exacerbation of COPD in the last year (severe acute exacerbation of COPD is an event requiring hospitalization or emergency room visit)

GOLD Classification of the Severity of COPD

- GOLD 1: Mild FEV$_1$ ≥80% of predicted
- GOLD 2: Moderate 50% ≤FEV$_1$ <80% of predicted
- GOLD 3: Severe 30% ≤FEV$_1$ <50% of predicted
- GOLD 4: Very Severe FEV$_1$ <30% of predicted

Note: Use COPD Assessment Tool for comprehensive assessment of symptoms, weak correlation between FEV$_1$ and symptoms

Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease
Cochrane DB Syst Rev 2014;9:CD001228
Study: Cochrane systematic review 16 studies.
Population: 1787 patients with acute COPD exacerbations.
Intervention: Oral or parenteral corticosteroids vs. placebo.
Outcome: Treatment failure, risk of relapse, time to next COPD exacerbation, likelihood of adverse event, length of hospital stay, and lung function at end of treatment.
Results: Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n=917) with median treatment duration 14 d, odds ratio (OR) 0.48 (95% CI 0.35-0.67). There was moderate-quality evidence for a lower rate of relapse at 1 mo for treatment with systemic corticosteroid in two studies (n=415) (hazard ratio (HR) 0.78; 95% CI 0.63-0.97). Mortality up to 30 d was not reduced by treatment with systemic corticosteroid compared with control in 12 studies (n=1319; OR 1.00; 95% CI 0.60-1.66). FEV1, measured up to 72 h, showed significant increase (7 studies; n=649; mean difference (MD) 140 mL; 95% CI 90-200); however, this benefit was not observed at later time points. The likelihood of adverse events increased with corticosteroid treatment (OR 2.33; 95% CI 1.59-3.43). The risk of hyperglycemia was significantly increased (OR 2.79; 95% CI 1.86-4.19). For general inpatient treatment, duration of hospitalization was significantly shorter with corticosteroid treatment (MD -1.22 d; 95% CI -2.26 to -0.18), with no difference in length of stay in the intensive care unit (ICU) setting. Comparison of parenteral vs. oral treatment showed no significant difference in the primary outcomes of treatment failure, relapse, mortality or for any secondary outcomes.
Conclusion: Treatment of COPD exacerbations with systemic corticosteroid by the oral or parenteral route may reduce treatment failure and relapse at 1 mo and length of hospital stay and results in earlier improvement in lung function. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid on treatment failure, relapse or mortality. There is an increase in adverse drug effects with corticosteroids treatment, which is greater with parenteral administration compared with oral treatment.

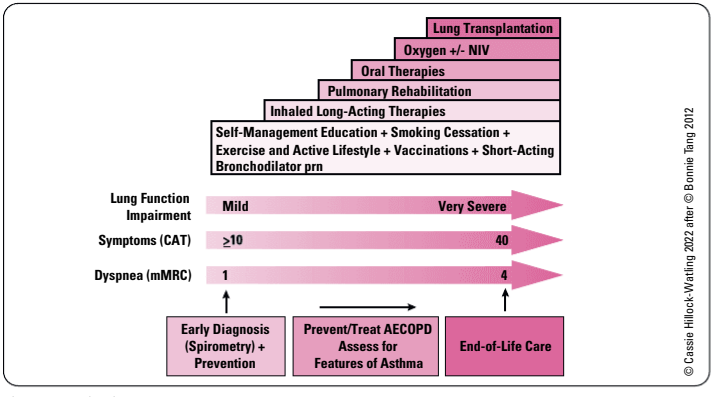


Figure 10. Guidelines for COPD management
Adapted from: Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence. Can J Respir Crit Care Sleep Med 2019; 3:4, 210-232

Acute Exacerbations of COPD

- definition
  - sustained (>48 h) worsening of dyspnea, cough, or sputum production, often leading to an increased use of rescue medications
  - in addition, defined as either purulent or non-purulent (to predict need for antibiotic therapy)
- etiology: viral URTI, bacteria, air pollution, CHF, PE, MI
- management
  - ABCs, consider NIV early if high CO_2 and/or reduced pH
  - O_2: target 88-92% SaO_2 for CO_2 retainers
  - bronchodilators by MDI with spacer or nebulizer
  - SABA + anticholinergic, e.g. salbutamol and ipratropium bromide via nebulizers
  - systemic corticosteroids: oral prednisone (if absorption issue can use IV methylprednisolone)
  - antibiotics for purulent COPD exacerbations
  - patients with no risk factors for resistant organisms: any of doxycycline/macrolide/amoxicillin/etc.
  - patients with risk factors for resistant organisms: amoxicillin/clavulanic acid or respiratory fluoroquinolone
  - post exacerbation: rehabilitation within 2 wk if possible
- ICU admission
  - for life-threatening exacerbations
  - ventilatory support
  - non-invasive: NIPPV (BiPAP)
  - conventional mechanical ventilation

Prognosis in COPD

- prognostic factors
  - frequency and severity of acute exacerbations is the single best predictor
  - lung function tests and mMRC dyspnea scale add value
  - development of hypoxemia, hypercapnia, or cor pulmonale portend a poor prognosis
- 5 yr survival
  - FEV_1 <1 L = 50%
  - FEV_1 <0.75 L = 33%
- BODE index for risk of death in COPD
  - greater score = higher probability the patient will die from COPD; score can also be used to predict hospitalization
  - 10 point index consisting of four factors:
    - Body mass index (BMI): ≤21 (+1 point)
    - Obstruction (FEV_1): 50-64% (+1), 36-49% (+2), <35% (+3)
    - Dyspnea (mMRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
    - Exercise capacity (6 min walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)

Dual Combination Therapy vs. Long-Acting Bronchodilators Alone for Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review and Network Meta-Analysis
Cochrane DB Syst Rev 2018; CD012620.
Study: Cochrane systematic review of 99 studies
Population: 101311 participants with moderate to severe COPD.
Intervention: Four different groups of inhalers (i.e. LABA/LAMA combination, LABA/ICS combination, LAMA and LABA).
Outcomes: COPD exacerbations (moderate to severe and severe), symptom and quality-of-life scores, safety outcomes, and lung function.
Result: LABA/LAMA combination therapy is most effective in reducing COPD exacerbations, followed by LAMA in high-risk and low-risk populations. LABA/LAMA decreases moderate-to-severe exacerbations compared to LABA/ICS (HR 0.86; 95% credible interval (CrI) 0.76-0.99), LAMA (HR 0.87; 95% CrI 0.78 to 0.99), and LABA in high-risk populations (HR 0.70; 95% CrI 0.61-0.80). LAMA decreases moderate-to-severe exacerbations compared to LABA in high-risk (HR 0.80; 95% CrI 0.71-0.88) and low-risk populations (HR 0.87; 95% CrI 0.78-0.97). LABA/LAMA decreases severe exacerbations compared to LABA/ICS (HR 0.78; 95% CrI 0.64-0.93) and LABA (HR 0.64; 95% CrI 0.51-0.81) in high-risk populations. There was a general trend of the combination therapies having greater improvement in symptom and quality of life scores compared to monotherapies. LABA/ICS was the lowest ranked for pneumonia serious adverse events in high-risk and low-risk populations. LABA/ICS increases the odds of pneumonia compared to LAMA/LABA (OR 1.69; 95% CrI 1.20-2.44), LAMA (OR 1.78; 95% CrI 1.33-2.39), LABA (OR 1.50; 95% CrI 1.17-1.92). The mean difference in lung function for LABA/LAMA versus LABA in high-risk population exceeded the minimal clinically important difference (mean difference 0.13 L; 95% CrI 0.10-0.15).
Conclusions: LABA/LAMA combination therapy is most effective in reducing COPD exacerbations. LAMA-containing therapies may be superior to therapies without LAMA at reducing COPD exacerbations. Combination therapies may be more effective than monotherapies for improving symptoms and quality of life scores. Therapies that contain ICS are associated with an increased risk of pneumonia. The mean difference in lung function when comparing LABA/LAMA versus LABA is significant.

Prevalence of Pulmonary Embolism Among Patients with COPD Hospitalized with Acutely Worsening Respiratory Symptoms
JAMA, 2021; 325(1):59-68
Purpose: To determine the prevalence of pulmonary embolism (PE) in patients with COPD admitted to the hospital for acutely worsening respiratory symptoms
Methods: Multicenter cross-sectional study with prospective follow-up conducted in 7 French hospitals. A predefined pulmonary embolism diagnostic algorithm based on Geneva score, D-dimer levels, and spiral computed tomographic pulmonary angiography plus leg compression ultrasound was applied within 48 h of admission; all patients had 3-month follow-up. Patients were recruited from January 2014 to May 2017 and the final date of follow-up was August 22, 2017.
Conclusion: Among patients with chronic obstructive pulmonary disease admitted to the hospital with an acute worsening of respiratory symptoms, pulmonary embolism was detected in 5.9% of patients using a predefined diagnostic algorithm.

Bronchiectasis

Definition
- irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently impaired mucous clearance and/or infected mucus
- usually affects medium sized airways
- the most common sputum pathogens found in patients with non-cystic fibrosis are *H. influenzae, P. aeruginosa, M. catarrhalis,* and *nontuberculous mycobacterium*

Table 16. Etiology and Pathophysiology of Bronchiectasis

Obstruction	Post-Infectious (results in dilatation of bronchial walls)	Impaired Defenses/Drainage (leads to chronic infections and inflammation)
Tumour Foreign body	Pneumonia TB Nontuberculous mycobacterium (NTM) Measles Pertussis	Hypogammaglobulinemia CF Defective leukocyte function Allergic bronchopulmonary aspergillosis Ciliary dysfunction (Kartagener's syndrome: bronchiectasis, sinusitis, situs inversus)

Signs and Symptoms
- chronic cough, copious purulent sputum (but 10-20% have dry cough), dyspnea, fatigue, chronic rhinosinusitis (for CF and primary ciliary dyskinesia), hemoptysis (can be massive), recurrent chest infections, local crackles (inspiratory and expiratory), rhonchi, wheezes
- may be difficult to differentiate from chronic bronchitis

Investigations
- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
  - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
  - specific: "tram tracking" – parallel narrow lines radiating from hilum, cystic spaces
- high-resolution thoracic CT (diagnostic, gold standard)
  - 87-97% sensitivity, 93-100% specificity
  - "signet ring": dilated bronchi with thickened walls where diameter of bronchus is >1.5x diameter of accompanying artery
- sputum cultures (routine + acid-fast bacillus)
- CBC
- LFTs
- immunoglobulin panel (serum Ig levels), α-1 antitrypsin level, immunology panel (ANA, ENAs), Rheumatoid factor, HIV test
- sweat chloride if cystic fibrosis is suspected (upper zone predominant, concomitant features)
- nasal nitric oxide and nasal ciliary biopsy if primary ciliary dyskinesia is suspected

Treatment
- vaccination: influenza and pneumococcal vaccinations
- chest physiotherapy, breathing exercises, physical exercise
- antibiotics (oral, IV, inhaled):
  - inhaled: used chronically to decrease bacterial load, in patients with frequent exacerbations, especially if *Pseudomonas* in sputum
  - oral/IV: routinely used for exacerbations, driven by sputum sensitivity when available; macrolides may be used for an anti-inflammatory effect chronically to reduce exacerbation frequency in patients with frequent exacerbations
- mucolytics (hypertonic saline)
- inhaled corticosteroids: only use if the patient has asthma or other co-existing disease as an indication
- oral corticosteroids have no role in chronic care or acute exacerbations
- pulmonary resection: in selected cases with focal bronchiectasis
- transplant: for end stage diffuse causes (e.g. primary ciliary dyskinesia, CF)

Cystic Fibrosis

- see Pediatrics, P92

Pathophysiology
- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, reproductive tract), and blockage of secretory ducts

Clinical Features
- multisystem clinical characteristics:
  - sinusitis, chronic pulmonary disease
  - pancreatic insufficiency, meconium ileus in children, distal ileal obstruction, liver disease, malnutrition
  - salt loss syndrome, azoospermia, CF-related DM, bone disease
- chronic lung infections

Canadian Thoracic Society Clinical Practice Guidelines on Long-term Non-invasive Ventilation for the Management of COPD
Can J Respir, Crit Care, Sleep Med 2021
Purpose: While non-invasive ventilation (NIV) has been shown to improve outcomes in acute COPD exacerbations with hypercapnic respiratory failure, the efficacy of long-term home NIV for COPD management is not as well studied. This document provides evidence-based recommendations for long-term home NIV in chronic hypercapnic COPD patients.
Methods: A panel of multidisciplinary clinical experts developed clinical questions using the PICO framework, performed a systematic review of the relevant literature, graded relevant evidence, and made clinical practice recommendations accordingly.
Conclusions: Long-term NIV improves survival and reduces hospital readmission in patients with stable COPD with significant hypercapnic respiratory failure. There is some evidence supporting the use of high-intensity ventilation over low-intensity ventilation. The task force supports the use of long-term NIV in this specific patient population.

Different Durations of Corticosteroid Therapy for Exacerbations of Chronic Obstructive Pulmonary Disease
Cochrane DB Syst Rev 2018;CD006897
Study: Cochrane systematic review. 8 studies.
Population: 582 patients, with severe or very severe COPD.
Intervention: Corticosteroids given at equivalent daily doses for 3-7 d (short duration) vs. 10-15 d (longer-duration).
Outcome: Treatment failure, risk of relapse, time to next COPD exacerbation, likelihood of adverse event, length of hospital stay, and lung function at end of treatment.
Results: In four studies there was no difference in risk of treatment failure between short-duration and longer-duration systemic corticosteroid treatment (n=457; odds ratio (OR) 0.72, 95% confidence interval (CI) 0.36-1.46). No difference in risk of relapse (a new event) was observed between short-duration and longer-duration systemic corticosteroid treatment (n=457; OR 1.04, 95% CI 0.70-1.56). Time to the next COPD exacerbation did not differ in one large study that was powered to detect non-inferiority and compared 5 d vs. 14 d of systemic corticosteroid treatment (n=311; hazard ratio 0.95, 95% CI 0.66-1.37). In five studies no difference in the likelihood of an adverse event was found between short-duration and longer-duration systemic corticosteroid treatment (n=503; OR 0.89, 95% CI 0.46-1.69. Length of hospital stay (n=421; mean difference (MD) -0.61 d, 95% CI -1.51-0.28) and lung function at the end of treatment (n=185; MD FEV1 -0.04 L; 95% CI -0.19-0.10) did not differ between short-duration and longer-duration treatment.
Conclusions: 5 d of oral corticosteroids is likely to be sufficient for treatment of adults with acute exacerbations of COPD, and this review suggests that the likelihood is low that shorter courses of systemic corticosteroids (of around 5 d) lead to worse outcomes than are seen with longer (10 to 14 d) courses.

- *S. aureus* and *H. influenzae*: early
- *P. aeruginosa*: most common in adulthood
- B. cepacia complex: worse prognosis (some subtypes) so infection control is key
- in adults, colonization with more resistant bacteria increases (e.g. PsA, *Burkholderia cepacia* complex, *Stenotrophomonas, Achromobacter,* MRSA, NTM etc.)

Investigations
- genetic testing
  - autosomal recessive- more than 2100 mutations in CFTR described, not all are disease causing
- sweat chloride test
  - increased concentrations of NaCl and $K^+[Cl^-]$ >60 mmol/L on two occasions supports the diagnosis)
  - single mutation carriers have normal sweat tests (and no disease)
- PFTs
  - early: airflow limitation in small airways
  - late: severe airflow obstruction, hyperinflation, gas trapping
- ABGs
  - hypoxemia, hypercapnia later in disease with eventual respiratory failure, and cor pulmonale
- CXR
  - hyperinflation, increased pulmonary markings (especially upper lobes)

Treatment
- chest physiotherapy
- pancreatic enzyme replacements, high fat, high calorie diet
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity): hypertonic saline, DNase
- inhaled antibiotics (tobramycin, colistin, aztreonam, levofloxacin, vancomycin)
- anti-inflammatory medications (e.g. azithromycin, ICS if concurrent asthma)
- antibiotics oral and IV (targeted to sputum growth if available, e.g. ciprofloxacin for Pseudomonas, if sensitive)
- CFTR potentiators and modulators (e.g. Ivacaftor, Orkambi®, Symdeko®)
- lung transplant

Prognosis
- worse prognosis associated with: frequent pulmonary exacerbations, rapid rate of decline of FEV 1, supplemental oxygen requirement with exercise or sleep, worsening malnutrition, infection with difficult to manage organism, CF-related DM, pneumothorax, massive hemoptysis
- female gender and low socioeconomic class have greater risk of early death

Usually presents in childhood as recurrent lung infections that become persistent and chronic

Correctors (Specific Therapies For Class II CFTR Mutations) for Cystic Fibrosis
Cochrane Database Syst. Rev. 2018;8:CD010966
Purpose: To evaluate the effects of cystic fibrosis transmembrane receptor (CFTR) correctors on clinically important outcomes, both benefits and harms, in children and adults with CF and class II CFTR mutations (most commonly F508del).
Methods: RCTs comparing CFTR correctors to placebo in people with CF class II mutations were searched in the Cochrane Cystic Fibrosis and Genetic Disorders Cystic Fibrosis Register. Two authors independently extracted data and assessed risk of bias and quality of evidence using GRADE criteria.
Results: The quality-of-life scores (respiratory domain) favoured combination therapy (both lumacaftor-ivacaftor and tezacaftor-ivacaftor) compared to placebo at all time points. The mean increase in cystic fibrosis questionnaire (CFQ) scores with twice-daily tezacaftor (100 mg) and ivacaftor (150 mg) was approximately 5 points (95% CI 3.20 to 7.00; 504 participants; moderate quality evidence). FEV1%-predicted improved with both combination therapies compared to placebo at 6 mo, by 5.21% with lumacaftor-ivacaftor OD (95% CI 3.61% to 6.80%; 504 participations; high quality evidence), and by 2.40% with lumacaftor-ivacaftor BID (95% CI 0.40% to 4.40%; 204 participants; low-quality evidence). More participants receiving the lumacaftor-ivacaftor combination reported early breathlessness (OR 2.05; 99% CI 1.10 to 1.83; 739 participants; high quality evidence). These adverse effects were not reported in the tezacaftor-ivacaftor studies.
Conclusions: Overall, the deployment of combination CFTR corrector therapies improve quality-of-life and lung function in patients with class II CF, compared to placebo controls. Adverse drug effects can be mitigated with the use of tezacaftor-ivacaftor, when clinically indicated.

Interstitial Lung Disease

Definition
- a group of disorders which cause diffuse parenchymal lung disease, with progressive scarring of lung tissue and impairment in lung function and gas exchange

Pathophysiology
- inflammatory and/or fibrosing process in the alveolar walls → distortion and destruction of normal alveoli and microvasculature
- typically associated with:
  - lung restriction (decrease in TLC and VC)
  - decreased lung compliance (increased or normal FEV1/FVC)
  - impaired diffusion (decreased DLCO)
  - hypoxemia due to V/Q mismatch (usually without hypercapnia until end stage)
  - pulmonary HTN and cor pulmonale occur with advanced disease secondary to hypoxemia and blood vessel destruction

Etiology
- IPF is the most common cause; however, there are numerous other causes including medication and connective tissue disorders
- a careful review of risk factors (e.g. organic/inorganic exposures, connective tissue disease symptoms, occupational history, medications) is needed during patient evaluation

In ILD think
FASSTand RAAIDS

Upper Lung Disease (FASST)
Farmer's lung (HP)
Ankylosing spondylitis
Sarcoidosis
Silicosis
TB

Lower Lung Disease (RAAIDS)
Rheumatoid Arthritis
Asbestosis
Amiodarone
IPF
Drugs
Scleroderma

Table 17. Interstitial Lung Diseases

Unknown Etiology	Known Etiology				
Idiopathic Interstitial Pneumonias	**ILD Associated with Connective Tissue Disorders**	**ILD Associated with Drugs or Treatments**	**Inherited Disorders**	**Granulomatous Disease**	**Other**
IPF (idiopathic pulmonary fibrosis)	Scleroderma	Antibiotics (nitrofurantoin)	Familial IPF	HP (usually organic antigen)	Langerhans-cell histiocytosis
NSIP (non-specific interstitial pneumonia)	Rheumatoid arthritis	Anti-inflammatory agents (methotrexate)	Telomerase mutations	Sarcoidosis	LAM (lymphangioleio-myomatosis)
RB-ILD (respiratory bronchiolitis related ILD)	Systemic lupus erythematosus (SLE)	Cardiovascular drugs (amiodarone)	Neurofibromatosis	Granulomatous lymphocytic ILD	Chronic eosinophilic pneumonia
DIP (desquamative interstitial pneumonia)	Polymyositis/ dermatomyositis Anti-synthetase syndromes	Antineoplastic agents (chemotherapy agents)	Tuberous sclerosis		Pneumoconioses (inorganic dust): Silicosis Asbestosis, Coal workers pneumoconiosis, Chronic beryllium disease
COP (cryptogenic organizing pneumonia)	Anti-synthetase syndromes, Polymyositis/ dermatomyositis	Recreational drugs (e.g. crack lung, talc granulomatosis)	Gaucher's disease		
AIP (acute interstitial pneumonia)	Mixed connective tissue disease	Radiation			
LIP (lymphocytic organizing pneumonia)	ANCA associated vasculitis				
IPPFE (idiopathic pleuroparenchymal fibroelastosis)	Sjogren's syndrome				
AFOP (acute fibrinous and organizing pneumonia)					

Signs and Symptoms

- dyspnea, especially on exertion
- nonproductive cough
- crackles (dry, fine, end-inspiratory)
- clubbing (especially in IPF and asbestosis)
- features of cor pulmonale
- note that signs and symptoms vary with underlying disease process
  - e.g. sarcoidosis is seldom associated with crackles and clubbing

Investigations

The CXR can be normal in up to 10% of patients with interstitial lung disease

- CXR (see Medical Imaging, MI4)
  - usually decreased lung volumes
  - reticular, nodular, or reticulonodular pattern (nodular <3 mm)
  - hilar/mediastinal adenopathy (bilateral especially in sarcoidosis)
  - honeycombing
- CT (see Medical Imaging, MI6)
  - four categories when interpreting CT imaging for idiopathic ILD
  - UIP – reticulation, subpleural and basal predominant, honeycombing ± traction bronchiectasis
  - probable UIP – reticulation, subpleural and basal predominant, traction bronchiectasis
  - indeterminate for UIP – subtle reticulation, subpleural and basal predominant ("early UIP"), CT features that do not suggest any specific etiology
  - alternative diagnosis to IPF – CT features of cysts, mosaic attenuation, predominant ground-glass opacity, profuse micronodules, centrilobular nodules, consolidation, mid or upper lung zone predominance, peribronchovascular distribution
- PFTs
  - restrictive pattern: decreased lung volumes and compliance
  - normal or increased FEV1/FVC, e.g. flow rates are often normal or high when corrected for absolute lung volume
  - DLCO decreased
- ABGs
  - hypoxemia and respiratory alkalosis may be present with progression of disease, as well as respiratory acidosis in later stages
- other
  - ANA, RF are universally performed, and anti-CCP, ANCA, and myositis antibodies are performed on a case-by-case basis in addition to serum-precipitating antibodies to inhaled organic antigens (HP)

- bronchoscopy with lavage in select cases
- surgical lung biopsy is considered in patients with CT imaging showing an indeterminate for UIP and alternative diagnosis to IPF pattern - transbronchial cryobiopsies are an emerging technology that may replace the role of surgical biopsy for ILD

Unknown Etiologic Agents

IDIOPATHIC PULMONARY FIBROSIS

Definition
- pulmonary fibrosis of unknown cause with UIP histology (found on biopsy or inferred from CT)
- a progressive, irreversible condition
- DDx: connective tissue disease associated-ILD, chronic HP, asbestosis, NSIP

Signs and Symptoms
- commonly presents over age 50, incidence rises with age; males > females
- dyspnea on exertion, nonproductive cough, late inspiratory fine crackles at lung bases, clubbing

Investigations
- labs (nonspecific, autoimmune serology usually negative)
- CXR: reticular or reticulonodular pattern with lower lung predominance; often see honeycombing in advanced disease
- high resolution CT: typical pattern is one of UIP; ground glass, consolidation, or nodules should not be prominent in IPF
- biopsy: only if patient has an indeterminate for UIP or alternative diagnosis to IPF pattern on CT imaging

Treatment
- acute exacerbation:
  - prednisone - minimal evidence
  - antibiotics and diuretics are considered on an individualized basis ± mechanical ventilation
- ongoing management:
  - antifibrotic therapy: pirfenidone or nintedanib
  - smoking cessation and pulmonary rehab ± O2
  - PPI if patient has reflux
  - lung transplantation for advanced disease
  - palliative care

CRYPTOGENIC ORGANIZING PNEUMONIA and ORGANIZING PNEUMONIA

Definition
- organizing pneumonia: an inflammatory process that involves the bronchioles and alveolar space, caused by connective tissue disease associated ILD, medications, or other triggers
- cryptogenic organizing pneumonia: organizing pneumonia without an identifiable cause

Signs and symptoms
- nonspecific cough, dyspnea, recurrent pneumonia, commonly fever and fatigue and may be associated with an acute flu-like illness
- symptoms present for <2 mo in most patients
- lack of response to empiric antibiotics for community acquired pneumonia
- COP: no history of connective tissue disease

Investigations
- CXR: round-glass opacities and patchy consolidation - usually bilateral, but can be unilateral, and can be migratory on serial X-rays
- high resolution CT: air space consolidation in patchy distribution is most common, but can be more nodular or ground glass density - "reverse halo" is a classic sign involving consolidation surrounding areas of ground glass
- labs: ANA, RF, creatine kinase, antitopoisomerase, anticentromere antibody, anti-double-stranded DNA, ANCA, myositis antibodies - assess for rheumatologic cause
- bronchoscopy with lavage to exclude infections or malignancy
- surgical lung biopsy or transbronchial cryobiopsy
- diagnosed based on consistent imaging in the correct clinical context

Treatment
- COP: Immunosuppression with steroids - often recurrent and may require long taper with steroids, typically for 6 mo
- other forms of organizing pneumonia: treatment can be longer or shorter than 6 mo (e.g. drug induced OP may improve with removal of the drug alone

Known Etiologic Agents

HYPERSENSITIVITY PNEUMONITIS

Definition
- HP, also known as extrinsic allergic alveolitis, is a spectrum of immune-mediated lung disorders occurring in response to an inhaled organic antigen or low molecular weight compounds such as drugs and chemicals

Pathogenesis
- two hit hypothesis: genetic susceptibility/environmental factors plus antigen exposure
- subacute and acute HP are mediated through immune complex formation and inflammation
- chronic HP results from type IV hypersensitivity reaction, T-cell mediated granulomatous inflammatory response

Etiology
- caused by sensitization to inhaled agents, usually organic dust
- exposure often related to occupation or hobby
  - farmer's lung (thermophilic *actinomycetes*)
  - bird breeder's/bird fancier's lung (immune response to bird antigen)
  - humidifier lung (*Aureobasidium pullulans*)
  - sauna taker's lung (*v* spp.)
  - metalworking fluid lung (e.g. machinists and metal parts manufacturing)
- may have no identified antigen; likely represents something in the home environment

Signs and Symptoms
- acute presentation: (4-6 h after exposure)
  - dyspnea, cough, fever, chills, malaise (lasting 18-24 h)
- subacute presentation: more insidious onset than acute presentation
- chronic presentation
  - insidious onset over years
  - dyspnea, cough, malaise, anorexia, weight loss

Investigations
- CXR
  - acute: diffuse infiltrates, predominantly upper lobe
  - chronic: predominantly upper lobe reticulonodular pattern
- PFTs: acute HP is often obstructive, subacute is obstructive/mixed, chronic is progressively restrictive
- in both acute and chronic HP, serum precipitins may be detectable (neither sensitive nor specific)
- bronchoscopy with lavage and differential cell count (lymphocytic predominant)
- biopsy: often required to distinguish from IPF

Histopathology
- acute HP triad: poorly formed granulomas, cellular bronchiolitis, interstitial lymphocytic infiltrate
- subacute/chronic HP: poorly formed granulomas and multinucleated giant cells are often seen, may be difficult to distinguish from UIP

Treatment
- early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
- systemic corticosteroids can relieve symptoms and speed resolution
- steroid-sparing agents (e.g. mycophenolate, azathioprine) are often used in setting of progressive disease despite steroids or to prevent steroid related side effects

SARCOIDOSIS

Definition
- idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
- characterized pathologically by non-necrotizing granulomas (although occasionally necrosis is present)
- numerous human leukocyte antigens and other genetic markers have been shown to play a role and familial sarcoidosis is now recognized

Epidemiology
- typically affects young and middle-aged patients
- higher incidence among people of African descent (in USA) and from northern latitudes (e.g. Scandinavia, Canada)

IPF Prevalence
- Age 35-44: 2-7 per 100000
- Age >75: 175 per 100000

See Landmark Respirology Trials table for more information on ASCEND, which details the efficacy and safety of oral Pirfenidone in patients with idiopathic pulmonary fibrosis

Most common presentation of sarcoidosis: asymptomatic CXR finding

Hilar adenopathy refers to enlargement of mediastinal lymph nodes which is most often seen by standard CXR as spherical/ellipsoidal and/or calcified nodes. If unilateral, think neoplasia, TB, or sarcoid. If bilateral, think sarcoid or lymphoma

Corticosteroids for Pulmonary Sarcoidosis
Cochrane DB Syst Rev 2005;2:CD001114
Study: Cochrane systematic review of 13 RCTs.
Population: 1066 participants with pulmonary sarcoidosis
Interventions: steroids (oral or inhaled) versus control
Outcomes: Improved CXR
Results: Oral steroids demonstrated an improvement in CXR (RR 1.46, 95% CI 1.01-2.09). For inhaled corticosteroids, two studies showed no improvement in lung function and one study showed an improvement in diffusing capacity. No data on side effects.
Conclusions: Oral steroids improve CXR findings and global scores of CXR, symptoms, and spirometry over 3-24 mo but do not improve lung function or modify disease course. Oral steroids may be of benefit for patients with Stage 2 and 3 disease.

CXR Fibrotic Patterns
Asbestosis: lower > upper lobes
Silicosis: upper > lower lobes
Coal: upper > lower lobes

Signs and Symptoms
- asymptomatic, cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
- chest exam often normal
- common extrapulmonary manifestations
  - eye involvement (anterior or posterior uveitis)
  - skin involvement (skin papules, erythema nodosum, lupus pernio)
  - peripheral lymphadenopathy
  - arthralgia
  - hepatomegaly ± splenomegaly
  - less common extra-pulmonary manifestations involve bone, CNS, kidney, cardiac (arrhythmias, sudden death, CHF)
- two acute sarcoid syndromes
  - Lofgren's syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
  - Heerfordt-Waldenstrom syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy

Investigations
- CBC (cytopenias from spleen or marrow involvement, lymphopenia common)
- serum electrolytes, creatinine, liver enzymes, calcium (hypercalcemia/hypercalciuria due to vitamin D activation by granulomas)
- hypergammaglobulinemia, occasionally RF positive
- elevated serum ACE (non-specific and non-sensitive) – reflects total body granuloma load
- CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
- PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased DLCO, or mixed obstructive/restrictive pattern
- ECG: to rule out conduction abnormalities
- slit-lamp eye exam: to rule out uveitis

Diagnosis
- biopsy
  - transbronchial lung biopsy, transbronchial lymph node aspiration, EBUS guided lymph node biopsy, or mediastinoscopic lymph node biopsy for granulomas
  - in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

Staging
- radiographic, based on CXR
  - Stage 0: normal radiograph
  - Stage I: bilateral hilar lymphadenopathy ± paratracheal lymphadenopathy
  - Stage II: bilateral hilar lymphadenopathy with pulmonary infiltration
  - Stage III: pulmonary infiltration alone (reticulonodular pattern or nodular pattern)
  - Stage IV: pulmonary fibrosis (loss of volume in upper lobes common, honeycombing uncommon)

Treatment
- observation if asymptomatic (85% of stage I resolve spontaneously within 2 yr, 50% of stage II resolve spontaneously within 5 yr)
- treatment for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
- first line treatment is prednisone
- methotrexate or other immunosuppressives can be used as adjuncts if steroid response is unsatisfactory or as steroid-sparing agents in those who do not tolerate steroids
- lung transplant in end-stage disease

Remember to involve occupational health and place of work for data collection and treatment plan.
Also counsel re: worker's insurance as per jurisdiction (e.g. Workers Safety Insurance Board (WSIB) in Ontario)

Prognosis
- mortality ranges from less than 1% to 8% depending on care setting, severity of disease, and patient demographics (e.g. age, ethnicity, and sex)

PNEUMOCONIOSES
- group of chronic lung diseases caused by exposure to mineral dusts, and organic dusts
- no effective treatment, therefore key is exposure prevention through the reduction of dust and the use of protective equipment
- recommend smoking cessation, annual influenza and pneumococcal vaccination, pulmonary rehabilitation, lung transplant for end-stage disease

Table 18. Pneumoconioses

Diagnosis	Etiology	Signs/Symptoms	Investigations	Complications
Asbestosis	Exposure risks: insulation, shipyard, construction, brake linings, pipe fitters, plumbers Slowly progressive diffuse interstitial fibrosis induced by inhaled asbestos fibres Usually requires >10-20 yr of exposure Latency period: 20-30 yr	Insidious onset Dyspnea Cough: paroxysmal, non-productive Clubbing (much more likely in asbestosis than silicosis or CWP)	CXR Lower > upper lobe Reticulonodular pattern, may develop IPF-like honeycombing Asbestos exposure can also cause pleural and diaphragmatic plaques (± calcification), pleural effusion, round atelectasis Microscopic examination reveals ferruginous bodies: yellow-brown rod-shaped structures which represent asbestos fibres coated in macrophages	Asbestos exposure increases risk of bronchogenic CA and malignant mesothelioma Risk of lung cancer dramatically increased for smokers
Silicosis	At risk population: sandblasters, rock miners, stone cutters, quarry and highway workers Generally requires >20 yr exposure; may develop with much shorter but heavier exposure	Dyspnea, cough, and wheezing	CXR Upper > lower lobe Early: nodular disease (simple pneumoconiosis), lung function usually normal Late: nodules coalesce into masses (progressive massive fibrosis) Possible hilar lymph node enlargement (frequently calcified), especially "eggshell" calcification	Mycobacterial infection (e.g. TB), chronic necrotizing aspergillosis, lung CA, rheumatic disorders, kidney disease, chronic airflow obstruction, and chronic bronchitis
Coal Workers' Pneumoconiosis	At risk population: coal workers, graphite workers (coal is less fibrogenic than silica)	Simple CWP No signs or symptoms, usually normal lung function - few patients progress to complicated CWP Complicated CWP (progressive massive fibrosis)	Simple CWP CXR: multiple nodular opacities, mostly upper lobe Pathologic hallmark is coal macule Complicated CWP CXR: opacities larger and coalesce	COPD, chronic renal failure, rheumatoid arthritis

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH DRUGS OR TREATMENTS

Drug-Induced

- antibiotics: nitrofurantoin, penicillin, sulfonamide
- cardiovascular drugs: amiodarone, tocainide
- anti-inflammatory agents: methotrexate, penicillamine, etanercept, gold salts
- recreational drugs (e.g. heroin, methadone)
- biologics: rituximab, anti-TNF-α agents (infliximab, etanercept, adalimumab), immunotherapy drugs
- chemotherapy/antineoplastic therapy (e.g. bleomycin)

Radiation-Induced

- acute pneumonitis: typically 4-12 wk post-exposure
- late fibrosis: 6-12 mo post-exposure
- infiltrates conform to the shape of the radiation field

Pulmonary Vascular Disease

Pulmonary Hypertension

Definition

- mean pulmonary arterial pressure >20 mmHg with a pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and peripheral vascular resistance (PVR) ≥3 Wood units measured by right heart catheterization in supine position at rest
- pulmonary HTN is grouped into 5 categories and classified based on etiology

Table 19. World Health Organization Classification of Pulmonary Hypertension and their Treatment Options

Classification	Some Causes	Treatment Options	Consider in All Patients with PH
I. Pulmonary Arterial HTN (PAH)	Idiopathic Hereditary mutations Collagen vascular disease (scleroderma, SLE, RA) Congenital heart disease (Eisenmenger syndrome) Persistent pulmonary hypertension of the newborn (PPHN) Portopulmonary HTN	CCBs for patients with vasoreactivity. Advanced therapy with single or combination prostanoids, endothelin receptor antagonists (ERA), PDE5 inhibitors. Lung transplantation for refractory advanced patients. Treatment of underlying condition if relevant	
	HIV infection Drugs and toxins (e.g. anorexigens) Schistosomiasis Pulmonary capillary hemangiomatosis Pulmonary veno-occlusive disease (PVOD)		Oxygen therapy Exercise Consider anticoagulation
II. Pulmonary HTN due to Left Heart Disease	Related to heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF) Left-sided valvular heart disease (e.g. aortic stenosis, mitral stenosis)	Treat underlying lung disease and/or cause of chronic hypoxia and correct with supplemental oxygen (proven mortality benefit)	Influenza and pneumococcal vaccines Counselling on pregnancy risks
	Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	Group I PH (PAH) therapies not applicable in Group III PH	Diuretic therapy in patients with signs of right ventricular failure and fluid retention
III. Pulmonary HTN due to Lung Disease and/or Hypoxia	Obstructive lung disease (COPD) Restrictive lung disease (e.g. ILD like idiopathic pulmonary fibrosis) Mixed restrictive/obstructive lung disease (e.g. lymphangioleiomyomatosis)	Treat underlying lung disease and/or cause of chronic hypoxia and correct with supplemental oxygen (proven mortality benefit)	
	Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep-disordered breathing, developmental lung disorders)	Group I PH (PAH) therapies not applicable in Group III PH	
IV. Chronic Thromboembolic Pulmonary HTN (CTEPH)	Chronic PE, other pulmonary artery obstruction (e.g. tumours, parasites, congenital stenosis) Thromboembolic obstruction of proximal pulmonary arteries	Anticoagulation, pulmonary thromboendarterectomy, riociguat	
V. Pulmonary HTN with Unclear Multifactorial Mechanisms	Hematologic disorders (e.g. sickle cell) Systemic disorders (e.g. sarcoidosis) Metabolic disorders Extrinsic compression of central pulmonary veins (tumour, adenopathy, fibrosing mediastinitis) Segmental pulmonary hypertension	Treat underlying cause	

Adapted: Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classifications of pulmonary hypertension. Eur Respir J 2019;53:1801913. Table 2

Guidelines for Vasodilator Response in Pulmonary Arterial HTN
Selected patients with pulmonary arterial hypertension (PAH) that respond to vasodilators acutely, have an improved survival with long-term use of high dose CCBs
Vasoreactivity testing: short-acting agent such as IV epoprostenol, IV adenosine, or inhaled NO
Positive vasodilator response: decrease in mean pulmonary arterial pressure (mPAP) ≥10 mmHg to <40 mm Hg and stable/increased cardiac output
Positive vasodilator response: should be considered as candidate for trial of oral CCB therapy
Canadian Cardiovascular Society/Canadian Thoracic Society Position Statement on Pulmonary Hypertension. Canadian Journal of Cardiology 2020;36:977-992

IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (PRIMARY PULMONARY HYPERTENSION)

Definition

- pulmonary HTN in the absence of a demonstrable cause (i.e. Group I)
- disease of the pulmonary artery vessel wall characterized by vasoconstriction, vascular proliferation, and obstructive remodeling leading to increased pulmonary vascular resistance

Pathology

- histology includes medial arterial hypertrophy, intimal fibrosis, and plexiform arteriopathy

Epidemiology

- usually older adults between the ages of 50 and 65, female predominance at younger ages
- most cases are sporadic; familial predisposition in <5% of cases, some linked to mutations in BMPR2

Pulmonary arterial pressures are measured by pulmonary artery catheters (i.e. Swan-Ganz catheter) which are inserted into a large vein (often internal jugular). A balloon at the end of the catheter tip is inflated causing the catheter to advance through the right side of the heart and into the pulmonary artery. This allows for the measurement of right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures as well as sampling of mixed venous blood. A thermistor near the end of the catheter also allows for assessment of cardiac output by thermodilution

Signs and Symptoms

Table 20. Signs and Symptoms of Pulmonary Hypertension

Symptoms	Signs
Dyspnea	Loud, palpable P2
Fatigue	RV heave
Retrosternal chest pain	Right-sided S4 (due to RVH)
Syncope	Systolic murmur (tricuspid regurgitation (TR))
Symptoms of underlying disease	If right ventricular failure: right sided S3, increased JVP, positive hepatojugular reflux, peripheral edema, TR
Peripheral Edema	Signs of underlying disease
Palpitations	

*Physical exam may be unremarkable in early disease

Diagnosis
- exclude:
  - left heart disease
  - lung disease
  - chronic thromboembolic disease
  - diseases in Group V PH
  - known causes of Group I PAH
    - connective tissue diseases
    - drugs/toxins
    - congenital heart disease
    - HIV
    - schistosomiasis
    - liver disease
    - heritable disease
    - PVOD/pulmonary capillary hemangiomatosis (PCH)

Investigations
- CXR: enlarged central pulmonary arteries, cardiac changes due to right ventricular enlargement (filling of retrosternal air space)
- ECG: RVH/right-sided strain (see Cardiology and Cardiac Surgery, C7)
- 2-D echo doppler assessment of right ventricular systolic pressure
- right heart catheterization: to confirm diagnosis through direct measurement of mean pulmonary arterial pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, and cardiac output
- PFTs to assess for underlying lung disease: DLCO usually reduced; volumes and flows normal
- CT angiogram to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary HTN; other serologic markers can be used in the appropriate clinical setting
- routine blood work: biochemistry, CBC, TSH, liver function tests, possible HIV test

Treatment
- treatment depends on classification (see *Table 19, R19*)

Prognosis
- morbidity and mortality are high but depend on underlying condition
- survival decreases to approximately 1 yr if severe pulmonary HTN (with rapid progression of symptoms, frequent syncope, and advanced WHO functional class), or right heart failure

Pulmonary Embolism

Definition
- mechanical obstruction of the pulmonary vasculature leading to obstruction of blood flow
- can be classified as acute, subacute, or chronic depending on presentation of symptoms relative to time after initial event
  - an acute PE can also be classified as massive, sub-massive, or low-risk PE

Etiology and Pathophysiology
- lower extremity deep vein thrombi are the source of most clinically recognized PEs
- less common causes include fat emboli, septic emboli, amniotic fluid emboli, tumour thrombi, and air emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE

Epidemiology
- one of the most common causes of preventable death in the hospital

Multidetector Computed Tomography for Acute Pulmonary Embolism (PIOPED II Trial)
NEJM 2006;354:2317-2327
Study: Multicentre, prospective study
Population: 824 patients with clinically suspected acute PE
Measurements: Accuracy of multidetector CTA alone and combined with venous-phase imaging.
Outcomes: Diagnosis of PE.
Results: 773 of 824 patients had adequate CTAs for interpretation. PE was diagnosed in 192 of the 824 patients. Sensitivity was 83% (150 of 181 patients, 95% CI 0.76-0.92) and specificity was 96% (567 of 592 patients, 95% CI 0.93-0.97). However, the predictive value of CTA-CTV varied when clinical pre-test probability was taken into account. PPV of CTA for high, intermediate and low clinical probability were 96% (95% CI 0.78-0.99), 92% (95% CI 0.84-0.96), and 58% (95% CI 0.40-0.73), respectively. NPV of CTA for high, intermediate, and low clinical probability were 60% (95% CI 0.32-0.83), 89% (95% CI 0.82-0.93), and 96% (95% CI 0.92-0.98) respectively.
Conclusion: CTA is effective for diagnosing or excluding PE in accordance with assessment of clinical pretest probability. When clinical probability is inconsistent with imaging results, further investigations are required to rule out PE.

D-dimer is elevated in patients with increased age, recent surgery, CA, inflammation, infection, pregnancy, and severe renal dysfunction. It has good sensitivity and negative predictive value, but poor specificity and positive predictive value

Classic ECG finding of PE is S1-Q3-T3 (inverted T3), but most commonly only sinus tachycardia is seen

Clinical Prediction Rule for Pulmonary Embolism
J Thromb Hemost 2000;83:416-420

Wells' Criteria

Risk Factors	Points
Clinical signs of DVT	3.0
No more likely alternative diagnosis	3.0
Immobilization or surgery in previous 4 wk	1.5
Previous PE/DVT	1.5
HR >100 beats/min	1.5
Hemoptysis	1.0
Malignancy	1.0
Clinical Probability	
Low (0-2)	3%
Intermediate (3-6)	28%
High (>6)	78%

Modified Wells': >4 PE likely; ≤4 PE unlikely
JAMA 2006

Virchow's Triad
Venous stasis
Endothelial cell damage
Hypercoagulable states

- VTE affects approximately 1-2 in 1000 adults per yr with approximately one third of first VTE presentations being due to PE

Risk Factors

- stasis
  - immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
  - obesity, CHF
  - chronic venous insufficiency
- endothelial cell damage
  - postoperative injury, trauma
- hypercoagulable states
  - underlying malignancy (particularly adenocarcinoma)
  - CA treatment (chemotherapy, hormonal)
  - exogenous estrogen administration (oral contraceptive pill, hormone replacement therapy)
  - pregnancy, post-partum
  - prior history of DVT/PE, family history
  - nephrotic syndrome
  - coagulopathies: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease
- increasing age

Investigations (if highly suspicious, go straight to CT pulmonary angiogram)

- see Emergency Medicine, ER33

Table 21. Common Investigations for Pulmonary Embolism

Investigation	Purpose/Utility
Pulmonary Angiography (Gold Standard)	Filling defect indicative of embolus; negative angiogram excludes clinically relevant PE
	More invasive, and harder to perform than CT, therefore done infrequently
D-Dimer	Highly sensitive D-dimer result can exclude DVT/PE if pretest probability is already low
	Little value if pretest probability is high
	If D-dimer positive, will need further evaluation with compression U/S (for DVT) and/or CT (for PE)
CT Angiogram	Both sensitive and specific for PE
	Diagnosis and management uncertain for small filling defects
	CT may identify an alternative diagnosis if PE is not present
	CT scanning of the proximal leg and pelvic veins can be done at the same time and may be helpful
Venous Duplex U/S or Doppler	With leg symptoms
	Positive test rules in proximal DVT
	Negative test rules out proximal DVT
	Without leg symptoms
	Positive test rules in proximal DVT
	Negative test does not rule out a DVT: patient may have non-occlusive or calf DVT
ECG	Findings not sensitive or specific
	Sinus tachycardia most common; may see non-specific ST segment and T wave changes
	RV strain, RAD, right bundle branch block (RBBB), S1-Q3-T3 with massive embolization
CXR	Frequently normal; no specific features
	Atelectasis (subsegmental), elevation of a hemidiaphragm
	Pleural effusion: usually small
	Hampton's hump: cone-shaped area of peripheral opacification representing infarction
	Westermark's sign: dilated proximal pulmonary artery with distal oligemia/decreased vascular markings (difficult to assess without prior films)
	Dilatation of proximal pulmonary artery: rare
V/Q Scan	Very sensitive but low specificity
	Order scan if:
	CXR normal, no COPD
	Contraindication to CT (contrast allergy, renal dysfunction, pregnancy)
	Avoid V/Q scan if:
	CXR abnormal or COPD
	Inpatient
	Suspect massive PE
	Results:
	Normal: excludes the diagnosis of PE
	High probability: most likely means PE present, unless pre-test probability is low
	60% of V/Q scans are nondiagnostic
Echocardiogram	Useful to assess for RV strain due to massive or chronic PE
	No diagnostic use in PE (insensitive and nonspecific)
ABG	May show respiratory alkalosis (due to hyperventilation)
	May show respiratory alkalosis (due to hyperventilation)

PE Rule Out Criteria (PERC)
Prospective Multicentre Evaluation of the Pulmonary Embolism Rule Out Criteria
J Thromb Hemost 2008;6:772
- Age less than 50 yr
- Heart rate less than 100 bpm
- Oxyhemoglobin saturation ≥95 percent
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery or trauma requiring hospitalization within the past 4 wk

Acute PE can probably be excluded without further diagnostic testing if the patient meets all PERC criteria AND there is a low clinical suspicion for PE, according to either the Wells' criteria or a low gestalt probability determined by the clinician prior to diagnostic testing for PE.

Evaluation of a Suspected Pulmonary Embolism
Low clinical probability of embolism
D-dimer (+ve) → CT scan (+ve) → ruled in
(–ve) → ruled out
Intermediate or high probability
CT pulmonary angiography scan
(–ve) → ruled out
(+ve) → ruled in
Notes:
- Use D-dimers only if low clinical probability, otherwise, go straight to CT
- If using V/Q scans (CT contrast allergy or renal failure):
  - Negative V/Q scan rules out the diagnosis
  - High probability V/Q scan only rules in the diagnosis if high clinical suspicion
  - Inconclusive V/Q scan requires leg U/S to look for DVT or CT

Workup for Idiopathic Venous Thromboembolism
Thrombophilia workup: recurrent or idiopathic DVT/PE, age <50, FMHx, unusual location, massive
Malignancy workup: 12% of patients with idiopathic VTE will have a malignancy

The Use of Unfractionated Heparin Should Be Limited to:
- Patients with severe renal dysfunction (CrCl <30 ml/min) in whom LMWH and novel oral anticoagulation should be avoided
- Patients at elevated risk of bleeding that may need rapid reversal of anticoagulation
- Patients who receive thrombolytic therapy

See Landmark 10M Respirology Trials table for more information on EPSTEIN-CHOICE which details the efficacy of rivaroxaban vs. ASA in patients with VTE who completed a 6-12 mo course of anticoagulation therapy.

Treatment

- admit for observation and stratify risk – in low-risk PE setting with no other indication for hospitalization and low-risk of early adverse outcomes, patients may be sent home with anticoagulation
- oxygen: supplemental oxygen should be administered to target an oxygen saturation ≥90%
- pain relief: analgesics if chest pain – narcotics or acetaminophen
- acute anticoagulation: therapeutic-dose SC LMWH or fondaparinux or unfractionated heparin or oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) or direct thrombin inhibitors (dabigatran) – start ASAP
  - anticoagulation stops clot propagation, prevents new clots, and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months
  - obtain baseline CBC, INR, aPTT ± renal function ± liver function
  - for SC LMWH: dalteparin 200 U/kg once daily, enoxaparin 1 mg/kg BID, or fondaparinux 5-10 mg once daily – no lab monitoring – avoid or reduce dose in renal dysfunction
  - for IV heparin: bolus of 75 U/kg (usually 5000 U) followed by infusion starting at 20 U/kg/h – aim for aPTT 2-3x control
- long-term anticoagulation
  - for most nonpregnant patients who do not have renal insufficiency or active cancer, first-line is direct oral anticoagulants (rivaroxaban, apixaban, edoxaban, or dabigatran) rather than warfarin
  - if using warfarin instead of DOAC: start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 d and until INR in target range of 2-3 for at least 2 d (use for patients with severe renal insufficiency)
  - LMWH instead of warfarin for pregnancy, active cancer, or high bleeding risk patients
  - duration:
    - if reversible cause for PE (e.g. surgery, injury, pregnancy, etc.): 3-6 mo
    - if PE unprovoked: 6 mo to indefinite
    - if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite
- IV thrombolytic therapy
  - if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
  - hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding
  - massive PE may be treated with catheter-directed thrombolysis by an interventional radiologist, but catheter-directed thrombolysis is not recommended over systemic thrombolysis
- IVC filter: routine use is not indicated; use if recent proximal DVT and absolute contraindication to anticoagulation

Direct Oral Anticoagulants Compared with Vitamin K Antagonists (VKAs) for Acute Venous Thromboembolism: Evidence from Phase 3 Trials
Blood 2014;124:1968-1975
Study: Meta-analysis of six phase 3 randomized controlled trials
Population: 27023 patients with VTE
Intervention: DOACs versus VKAs
Outcomes: Overall efficacy, safety profile, and net clinical benefit for the treatment of acute symptomatic VTE
Results: Recurrent VTE occurred in 2.0% of DOAC recipients compared with 2.2% in VKA recipients (RR 0.90, 95% CI 0.77-1.06). Treatment with a DOAC significantly reduced the risk of major bleeding (RR 0.61, 95% CI 0.45-0.83).
Conclusions: DOACs and VKAs have a similar efficacy in the treatment of acute symptomatic VTE; however, treatment with a DOAC significantly reduces the risks of major bleeding.

Thromboprophylaxis

- cost-effective and mandatory for most hospital patients: reduces DVT, PE, all-cause mortality
- start ASAP
- continue at least until discharge or recommend extending for 35 d postoperatively, if major orthopaedic surgery

Table 22. VTE Risk Categories and Prophylaxis (see Hematology, H36)

Risk Group	Prophylaxis Options
Low Thrombosis Risk	
Medical patients: fully mobile	No specific prophylaxis
Surgery: <30 min, fully mobile	Frequent ambulation
Moderate Thrombosis Risk	
Most general, gynaecologic, urologic surgery	LMWH
Sick medical patients	Low dose unfractionated heparin
	Fondaparinux
High Thrombosis Risk	
Arthroplasty, hip fracture surgery	LMWH
Major trauma, spinal cord injury	Fondaparinux
	Warfarin (INR 2-3)
	Dabigatran
	Apixaban
	Rivaroxaban
	Low dose unfractionated heparin
High Bleeding Risk	
Neurosurgery, intracranial bleed	TED stockings™, pneumatic compression devices
Active bleeding	LMWH or low dose heparin when bleeding risk decreases

Pulmonary Vasculitis

Table 23. Pulmonary Vasculitis

Disease	Definition	Pulmonary Features	Extra Pulmonary Features	Investigations	Treatment
Granulomatosis with Polyangiitis (GPA, previously Wegener's Granulomatosis) (see Nephrology, NP24, NP25, and NP27)	Systemic vasculitis of medium and small arteries, most common pulmonary vasculitis	Necrotizing granulomatous lesions of the respiratory tract, which may lead to tracheal and/or bronchial stenosis, nodules, ILD, or alveolar hemorrhage	Focal necrotizing lesions of arteries and veins; may have nasal, sinus, and ear disease; crescentic glomerulonephritis	CXR/CT: nodules, cavities, and alveolar opacities c-ANCA (positive in 90% of cases) PR3 Tissue confirmation Urinalysis: look for abnormal sedimentation	Corticosteroids and cyclophosphamide or rituximab Plasma Exchange (PLEX) is also used often in cases of pulmonary hemorrhage, severe renal failure, or concomitant anti-GBM Prognosis with treatment is generally good (65-90% achieve full remission)
Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg-Strauss)	Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia	Asthma (prodromal phase, usually occurs before other systemic features) Eosinophilic infiltrates in small-and- medium sized vessels	Life-threatening systemic vasculitis involving the lungs, pericardium and heart, kidneys, skin, and PNS (mononeuritis multiplex)	CXR can often be normal (30-60%) but can see transient, patchy opacities Peripheral eosinophilia is the most common finding p-ANCA, myeloperoxidase (MPO) may be positive Biopsy involved tissue	Corticosteroids Cyclophosphamide (Use Five Factor Score to determine need) or rituximab With treatment, 90% of patients have clinical remission
Anti-GBM Disease (Goodpasture's) (see Nephrology, NP24)	A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung	Alveolar hemorrhage, which may present with dyspnea, cough, hemoptysis May follow influenza infection	Anemia Acute renal failure	CXR: may see alveolar infiltrates ELISA test with anti-GBM antibodies Renal biopsy/indirect immunofluorescence shows linear staining	Acutely: corticosteroids, plasmapheresis, immunosuppressive therapy (first line cyclophosphamide)
Systemic Lupus Erythematosus, Rheumatoid Arthritis, Scleroderma	See Rheumatology, RH11, RH8, and RH14				

Pulmonary Edema

- see Cardiology and Cardiac Surgery, C42

Diseases of the Mediastinum and Pleura

Mediastinal Masses

- see General and Thoracic Surgery, GS20

DDx of an Anterior Compartment Mass

4 Ts
Thymoma
Thyroid enlargement (goiter)
Teratoma and other germ cell tumors
Terrible lymphoma

Mediastinitis

- most common causes: postoperative complications of cardiovascular or thoracic surgical procedures

Acute

- etiology
  - perforation of esophagus or trachea – vomiting (Boerhaave's syndrome), penetrating trauma, foreign body, instrumentation, erosion (e.g. carcinoma, infection)
  - direct extension of infection – dental, lung, pleura, pericardium, lymph nodes, paraspinous, pancreatic
  - postoperative (sternotomy or mediastinoscopy)
  - primary mediastinal infections (e.g. inhalational anthrax)
- signs and symptoms
  - fever, substernal pain; often a dramatic and acute onset of symptoms, with irritability, restlessness, and a sense of impending doom
  - pneumomediastinum, mediastinal compression
  - mman's sign (auscultatory "crunch" during cardiac systole)
- treatment
  - antibiotics (IV vancomycin + 3rd gen cephalosporin), drainage, ± surgical closure of perforation

Mediastinal Components
Anterior: sternum to pericardium and great vessels. Includes: thymus, extrapericardial aorta and branches, great veins, lymphatic tissues
Middle: pericardium (anteriorly), posterior pericardial reflection, diaphragm, thoracic inlet. Includes: heart, intrapericardial great vessels, pericardium, trachea
Posterior: posterior pericardial reflection, posterior border of vertebral bodies, first rib to the diaphragm. Includes: esophagus, vagus nerve, thoracic duct, sympathetic chain, azygous venous system

Pleural Effusions

Definition
- excess amount of fluid in the pleural space

Etiology
- disruption of normal equilibrium between pleural fluid formation/entry and/or pleural fluid absorption/exit
- pleural effusions are classified as transudative or exudative
  - distinguish clinically using Light's Criteria (98% sensitivity and 83% specificity for identifying exudative pleural effusions)

Table 24. Laboratory Values in Exudative Pleural Effusion

	Light's Criteria	Modified Light's Criteria
Protein – Pleural/Serum	>0.5	>0.5
LDH – Pleural/Serum	>0.6	>0.6
Pleural LDH	>2/3 upper limit of N serum LDH	>0.45 upper limit of N serum LDH
Exudate = any one criterion		

Ann Intern Med 1979;77:507-513
Chest 1997;111:970-980

Transudative Pleural Effusions
- pathophysiology: alterations to Starling forces affects the rates of formation and absorption of pleural fluid
- etiology
  - CHF: usually bilateral, right-sided more than the left, can occasionally be isolated right-sided
  - cirrhosis leading to hepatic hydrothorax (diaphragmatic deficit allows fluid into chest cavity)
  - nephrotic syndrome, protein-losing enteropathy
  - pulmonary embolism (may cause transudative but more often causes exudative effusion)
  - peritoneal dialysis with transdiaphragmatic flow, hypothyroidism, urinothorax

Exudative Pleural Effusions
- pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction

Table 25. Exudative Pleural Effusion Etiologies

Etiology	Examples
Infectious	Parapneumonic effusion (associated with bacterial pneumonia, or other process such as lung abscess)
	Empyema: bacterial, fungal, TB
	TB pleuritis
	Viral infection (rare)
	Fungal
	Parasitic
Malignancy	Lung carcinoma (35%)
	Lymphoma (10%)
	Pulmonary Metastases: breast (25%), ovary, kidney, other
	Mesothelioma
	Myeloma
Inflammatory	Collagen vascular diseases: RA, SLE
	Pancreatitis
	Benign asbestos related effusion
	Pulmonary embolism
	Post-coronary artery bypass grafting or cardiac injury
	Drug reaction
Intra-Abdominal	Subphrenic abscess (sympathetic effusion)
	Pancreatic pseudocyst with fistula into pleural space (associated with elevated pleural fluid amylase)
	Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour) (can also be a transudate)
Intra-Thoracic	Esophageal perforation (associated with elevated pleural fluid salivary amylase)
Trauma	Hemothorax: rupture of a blood vessel, commonly by trauma or tumours
	Pneumothorax: spontaneous, traumatic
	Chylothorax (thoracic duct leak)
	Iatrogenic
Other	Drug-induced
	Hypothyroidism (can also be transudate)

Appearance of Pleural Fluid
- Bloody: trauma, malignancy, traumatic tap
- White: empyema, chylous, or chyliform effusion
- Black: aspergillosis, amoebic liver abscess
- Yellow-green: rheumatoid pleurisy
- Viscous: malignant mesothelioma
- Ammonia odour: urinothorax
- Food particles: esophageal rupture

Starling's hypothesis: The rate of passive fluid movement across a capillary wall is governed by the gradients of hydrostatic pressure and oncotic pressure across the same capillary wall

Transudative effusions are usually bilateral, not unilateral

Exudative effusions can be bilateral or unilateral

Signs and Symptoms

- often asymptomatic
- dyspnea: varies with size of effusion and underlying lung function
- pleuritic chest pain, shoulder pain (referred pain from the phrenic nerve, C3-C5, which innervates the diaphragm)
- inspection: ipsilateral decreased expansion; when accumulated rapidly, trachea can deviate away from effusion
- palpation: decreased tactile fremitus
- percussion: dullness
- auscultation: decreased breath sounds; bronchial breathing and egophony just above fluid level, sometimes pleural friction rub if inflammatory cause and minimal fluid

Investigations

- CXR
  - must have >200 mL of pleural fluid for visualization on PA film
  - PA: blunting of lateral costophrenic angle
  - lateral: >50 mL leads to blunting of posterior costophrenic angle
  - dense opacification of lower lung fields with concave meniscus as fluid accumulates
  - decubitus: fluid will layer out unless effusion is loculated
  - supine: fluid will appear as general haziness over lung field
- CT: helpful in differentiating parenchymal from pleural abnormalities; identifying loculation, measuring density of fluid (higher density may indicate a hemothorax); contrast can detect pleural enhancement indicative of empyema and may identify underlying lung pathology causing effusion
- U/S: detects small effusions and can guide thoracentesis
- thoracentesis: indicated if pleural effusion is a new and concerning finding, if patient is unstable, and/or if patient has pneumonia and there is a concern about infected parapneumonic effusion; order blood work (serum LDH, glucose, protein, albumin) at the same time for comparison
  - risk of re-expansion pulmonary edema if >1.5 L of fluid is removed in one shot through a closed tap
  - inspect for colour, character, presence of pus, and odour of fluid
  - send fluid for analysis (see *Table 26*)
- pleural biopsy: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology non-diagnostic)

Role of CT in Pleural Effusion

- To assess for fluid loculation, pleural enhancement (when using contrast), thickening and nodules, parenchymal abnormalities, and adenopathy
- Can provide clues to help distinguish benign from malignant effusion
- May not distinguish empyema from parapneumonic effusion

Features of Mesothelioma

- Multiple pleural nodules
- Circumferential pleural thickening
- Pleural thickening >1 cm
- Mediastinal pleural involvement

Imaging Features of Empyema

- Parietal pleural thickening
- Pleural enhancement
- Concurrent thickening and enhancement of both the visceral and parietal pleural (split pleural sign)

Table 26. Analysis of Pleural Effusion

Measure	Purpose
Always order:	
Protein, LDH	Transudate vs. exudate
	LDH especially high (>1000 IU/L) in empyema, rheumatoid, malignancy
	Protein especially high in TB, myeloma
Gram Stain, Ziehl-Neelsen Stain (TB), Culture	Looking for specific organisms (can add Ziehl-Neelsen Stain if TB suspected)
Cell Count Differential	Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, RA) Eosinophilic (seen in pneumothorax, hemothorax, drug reactions, pulmonary embolism, eosinophilic granulomatosis with polyangiitis, asbestos-related, malignancy, parasitic, occasionally TB) High RBC count: mostly traumatic, malignancy, PE with infarction, TB, hemothorax
Cytology	Malignancy
Glucose	Low (fluid:serum <0.5) in rheumatoid, TB, empyema, malignancy, esophageal rupture
pH	Normally about 7.6
	Very low (<7.0) in empyema, TB, rheumatoid, malignancy, esophageal rupture
May order (depending on clinical suspicion):	
Albumin	Albumin gradient for higher specificity assessment for exudate (compared to Light's criteria alone)
Amylase	Pancreatitis, esophageal perforation, malignancy
Rheumatoid Factor, ANA, Complement	Collagen vascular disease (not validated so seldom used)
Triglycerides	Chylothorax from thoracic duct leakage, mostly due to trauma, or lymphoma
Cholesterol, chylomicrons	Distinguish between chylothorax and chyliform effusion (latter seen in inflammation, e.g. TB, RA)

Complicated Parapneumonic Effusion (needs drainage if any of these are present):

- Loculation
- >1/2 hemithorax of fluid
- pH ≤7.2
- Glucose ≤2.2 mmol/L
- LDH ≥1000
- Gram stain or culture positive
- Frank pus

Empyema (always needs drainage)
Frank pus on tap
May or may not be loculated, and will often fulfill many of the criteria of a Complicated Parapneumonic Effusion

Treatment

- thoracentesis
- tube drainage if required
- immediate tissue plasminogen activator (tPA)/deoxyribonuclease (DNase) instillation to improve drainage of infected effusions
- treat underlying cause
- consider indwelling pleural catheter or pleurodesis in refractory chronic effusions
- consultation with thoracic surgery for potential surgical management

When possible, organism-directed therapy, guided by culture sensitivities or local patterns of drug resistance, should be utilized

Complicated Parapneumonic Effusion

- see General and Thoracic Surgery, GS17

Empyema

- see General and Thoracic Surgery, GS17

Atelectasis

- see General and Thoracic Surgery, GS11

Pneumothorax

- see General and Thoracic Surgery, GS17

Asbestos-Related Pleural Disease

Etiology and Pathophysiology

- non-malignant manifestations of asbestos exposure:
  - BAPE (benign asbestos pleural effusion)
    - exudative effusion, typically ~10 yr after exposure, often resolves on its ownpleural cytology may be needed to distinguish from mesothelioma or pleural metastases from other malignancies
  - round atelectasis
    - commonly seen peripherally, due to asbestos-pleural disease
    - often with calcified pleural plaques and/or pleural thickening
    - marker of exposure; usually an asymptomatic radiologic finding
  - asbestosis (a parenchymal finding – not pleural)
    - lower lobe ILD (appears the same as IPF)

Need to Rule Out Life-Threatening Tension Pneumothorax

If pneumothorax with:

- Severe respiratory distress
- Tracheal deviation to contralateral side
- Distended neck veins (↑ JVP)
- Signs of hemodynamic instability (e.g. hypotension)

Do not perform CXR
Needs immediate treatment
See Emergency Medicine, ER11 and ER22

Mesothelioma

Etiology and Pathophysiology

- primary malignancy of the pleura
- decades after asbestos exposure (even with limited exposure)
- smoking not a risk factor, but asbestos exposure and smoking synergistically increase risk of lung cancer

Signs and Symptoms

- chest pain, dyspnea, cough, bloody pleural effusion, and weight loss
- there can be associated paraneoplastic syndromes (e.g. hypercalcemia, hemolytic anemia, hypoglycemia)

Investigations

- CT thorax
- biopsy (pleuroscopic or open)
- needle biopsy may seed needle tract with tumour

Treatment

- use of multidisciplinary team with trimodal treatment (e.g. chemotherapy, radiation, surgical resection)
- palliation is often needed because of poor prognosis

Respiratory Failure

Definition
- failure of respiratory system to maintain normal gas exchange (oxygen and carbon dioxide homeostasis)
- hypoxemia (PaO_2 <60 mmHg), hypercapnia ($PaCO_2$ >50 mmHg)
- acute vs. chronic (compensatory mechanisms activated)

Signs and Symptoms
- signs of underlying disease
- hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale (if chronic)
- hypercapnia: confusion, headache, dyspnea, drowsiness, asterixis, warm periphery, chemosis, plethora, increased ICP (secondary to vasodilatation)

Investigations
- ABGs
- CXR and/or CT
- pulmonary function tests (for chronic respiratory failure)

Hypoxemic Respiratory Failure

Definition
- PaO_2 decreased, $PaCO_2$ normal or decreased

Treatment
- reverse the underlying pathology
  - oxygen therapy: maintain oxygenation (if shunt present, supplemental O_2 is less effective) using O_2 delivery systems (see Anesthesia, A10)
- ventilation, BiPAP, and PEEP/CPAP (see Anesthesia, A11): positive pressure can recruit alveoli and redistribute pulmonary edema fluid
- improve cardiac output: ± hemodynamic support (fluids, vasopressors, inotropes) (increases O_2 delivery)

Table 27. Approach to Hypoxemia

Type of Hypoxemia	Settings	$PaCO_2$	A-aO_2	Oxygen Therapy	Ventilation, BiPAP, and PEEP	Increasing Cardiac Output
1. Low FiO_2	High altitude	N or ↓	N	Improves	No change	No change
2. Hypoventilation	Drug overdose, muscle weakness, obesity, hypoventilation syndrome	↑	N	Improves	Improves with ventilation	No change
3. Physiologic Shunt = V/Q mismatch with low V	ARDS, pneumonia	N or ↓	↑	Less effective	Improves	No change
4. Anatomic Shunt (Right to Left)	Ventricular septal defect	N or ↓	↑	No change	Can worsen by increasing shunt	Can worsen
5. Low Mixed Venous O_2 Content	Shock	↓	↑	Improves or no change	Can worsen by reducing cardiac output	Improves
6. Diffusion Impairment	ILD, emphysema	N	↑	Improves	Improves with positive pressure	No change or worsens

*Where "N" = within normal limits, A-aO_2 = Alveolar–arterial gradient
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Hpercapnic Respiratory Failure

Definition
- $PaCO_2$ increased, PaO_2 decreased

Pathophysiology
- increased CO_2 production: fever, sepsis, seizure, acidosis, carbohydrate load
- increased dead space (normal or increased minute ventilation, low alveolar ventilation): COPD, CF, chest wall disorder, dead space ventilation (rapid shallow breathing)
  - inefficient gas exchange results in inadequate CO_2 removal in spite of normal or increased minute ventilation
- hypoventilation (low minute ventilation)
  - restrictive process such as chest wall disorder (e.g. severe kyphoscoliosis)
  - central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (e.g. opiates, benzodiazepines)

Dead Space
- Ventilation without perfusion
- The opposite of shunt

Causes of Hypercapnia
- Low total ventilation
- High dead space ventilation
- High CO_2 production

- neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis
- muscle fatigue

Treatment
- reverse the underlying pathology
- if $PaCO_2$ >50 mmHg and pH <7.35 consider noninvasive or mechanical ventilation
- correct exacerbating factors
  - nasotracheal/endotracheal tube suction: clearance of secretions
  - bronchodilators: reduction of airway resistance
  - antibiotics: treatment of infections
  - reverse medications that may be contributing (e.g. narcotics)
- maintain oxygenation (see above)
- diet: increased carbohydrates can increase $PaCO_2$ in those with mechanical or limited alveolar ventilation; high lipids decrease $PaCO_2$

In chronic hypercapnia, supplemental O_2 may worsen hypoxemia by worsening V/Q mismatch, Haldane effect, and/or decreasing respiratory drive (in order of physiologic importance); but do not deny oxygen if the patient is hypoxic

In COPD patients with chronic hypercapnia ("CO_2 retainers"), provide supplemental oxygen to achieve target SaO_2 from 88-92%

Acute Respiratory Distress Syndrome

Definition
- clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
- The Berlin Criteria for ARDS
  - acute onset
    - within 7 d of a known clinical insult or of patient noticing new or worsening of respiratory symptoms
    - usually occurs within 72 h of presumed trigger
  - bilateral opacities consistent with pulmonary edema on either CT or CXR
  - not fully explained by cardiac failure/fluid overload, but patient may have concurrent heart failure
- objective assessment of cardiac function (e.g. echocardiogram) should be perfumed if no clear risk factors

Acute Lung Injury
ALI is an outdated term that has the same definition as ARDS but with a PaO_2/FiO_2 ≤300. The Berlin Definition removed ALI and replaced it with the term mild ARDS

Etiology
- direct lung injury
  - airway: aspiration (gastric contents, drowning), pneumonia, inhalation injury (oxygen toxicity, nitrogen dioxide, smoke)
  - circulation: embolism (fat, amniotic fluid), reperfusion injury
- indirect lung injury
  - circulation: sepsis, shock, trauma, blood transfusion, pancreatitis
  - neurogenic: head trauma, intracranial hemorrhage, drug overdose (narcotics, sedatives, tricyclic antidepressants)

Categorization of ARDS as Mild, Moderate or Severe – The Berlin Criteria

ARDS Severity	PaO_2/FiO_2 (mmHg)*	Mortality (95% CI)
Mild	200-300	27 (24-30)%
Moderate	100-200	32 (29-34)%
Severe	<100	45 (42-48)%

*on ≥5 cm H_2O PEEP, #P<0.001
JAMA 2012;307:2526-2533

Pathophysiology
- disruption of alveolar capillary membranes → leaky capillaries → interstitial and alveolar pulmonary edema → reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN

Clinical Course
A. Exudative Phase
- first 7 d of illness after exposure to ARDS precipitant
- alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
- patients develop dyspnea, tachypnea, increased work of breathing
  - these result in respiratory fatigue and eventually respiratory failure (see *Hypoxemic Respiratory Failure, R27*)

B. Fibroproliferative Phase
- after day 7
- may still experience dyspnea, tachypnea, fatigue, and hypoxemia
- most patients clinically improve and are able to wean off mechanical ventilation
- some patients develop fibrotic lung changes that may require long-term support on supplemental oxygen or even mechanical ventilation
- if fibrosis present, associated with increased mortality

Risk Factors for Aspiration Pneumonia

Categories	Examples
Decreased level of consciousness	Alcoholism
Upper GI tract disorders	Dysphagia, esophageal disorders
Mechanical instrumentation	Intubation, nasogastric tube, feeding tube
Neurologic conditions	Dementia, Parkinson's disease
Others	Protracted vomiting

Treatment
- based on ARDS Network (see *Landmark Respirology Trials, R36*)
- treat underlying disorder (e.g. antibiotics if infection present)
- mechanical ventilation using low tidal volumes (<6 mL/kg) to prevent barotrauma
  - use optimal amount of PEEP to keep airways open and allow the use of lower FiO_2
  - may consider using prone ventilation, ± inhaled nitric oxide, short term paralytics (<48 h) or ECMO (extracorporeal membrane oxygenation) if conventional treatment is failing
- fluids and inotropic therapy (e.g. dopamine, dobutamine) if cardiac output inadequate
- pulmonary-arterial catheter now seldom used for monitoring hemodynamics
- mortality: 30-40%, usually due to non-pulmonary complications

- sequelae of ARDS include residual pulmonary impairment, severe debilitation, polyneuropathy and psychological difficulties, which gradually improve over time
- most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity

Neoplasms

Lung Cancer

- see General and Thoracic Surgery, GS14

Approach to the Solitary Pulmonary Nodule

- see Medical Imaging, *Lung Abnormalities*, MI17
- see General and Thoracic Surgery, GS13

Sleep-Related Breathing Disorders

Hypoventilation Syndromes

Definition

- group of syndromes characterized by hypoventilation during sleep, though daytime hypercapnia may also be a feature
- superimposed sleep apnea may be present
- categories of hypoventilation syndromes include: medical disorders, lung parenchymal or airway disease (typically severe), chest wall disorder (deformity such as kyphoscoliosis), neurologic disorder (brainstem lesions), respiratory muscle weakness (neuromuscular disease, myopathy), medications (opiates and other sedatives), obesity-hypoventilation syndrome (Pickwickian syndrome: BMI >30 kg/m^2 and no other cause of hypoventilation identified), congenital central alveolar hypoventilation syndrome, idiopathic hypoventilation syndrome

Normal Respiratory Changes during Sleep

- Tidal volume decreases, leading to decreased minute ventilation
- $PaCO_2$ increases (due to decreased minute ventilation)
- Pharyngeal dilator muscles relax causing increased upper airway resistance

Treatment

- management of the underlying condition
- usually PAP therapy (frequently BiPAP, which delivers ventilation in addition to airway splinting)

Sleep Apnea

Definition

- episodic decreases in airflow during sleep
- quantitatively measured by the Apnea-Hypopnea Index (AHI) = # of apneas and hypopneas per hour of sleep
- sleep apnea generally accepted to be present if AHI ≥5 events/h
  - AHI: Mild OSA 5-15 events/h, Moderate 15-30 events/h, Severe >30 events/h

Classification

- obstructive sleep apnea
  - caused by transient, episodic obstruction of the upper airway
  - absent or reduced airflow despite persistent respiratory effort
- central sleep apnea (see Neurology, N49)
  - hypercapnic CSA caused by transient, episodic decreases in CNS drive to breathe, typically seen in patients with sleep hypoventilation syndromes (see *Hypoventilation Syndromes*)
  - hypocapnic CSA, most commonly Cheyne-Stokes breathing, typically seen in patients with congestive heart failure and sometimes stroke; characterized by a crescendo-decrescendo pattern of alternating apnea and hyperpnea
- some patients exhibit a combination of obstructive, central and, mixed apneas (sometimes referred to as "complex sleep apnea"). Typically this involves ventilatory overshoot following an obstructive apnea, resulting in hypocapnia, loss of respiratory drive, and consequently a central apnea

Apnea: reduction in airflow ≥90% from baseline, lasting for ≥10 s

Hypopnea: reduction in airflow ≥30% from baseline, lasting for ≥10 s, associated with oxygen desaturation ≥3% or EEG arousal

Hyperpnea: period of increased ventilation, typically in the context of resumption in breathing, following an apnea or hypopnea

Obstructive apnea: absent airflow despite respiratory effort, due to upper airway occlusion

Central apnea: absent airflow, due to absent or reduced respiratory effort

Mixed apnea: absent airflow, with features of both central and obstructive events

SLEEP TESTING

Polysomnography

- sleep study, usually in-laboratory with technologist in attendance
- evaluates sleep stages and arousals (using EEG, EOG, EMG), airflow, ribcage and abdominal movement, ECG, SaO_2, limb movements, snoring, body position, and video recording

- indications:
  - evaluation for suspected sleep disordered breathing in a patient with compatible symptoms or risk factors
  - evaluation for non-respiratory causes of excessive daytime sleepiness
  - evaluation of selected cases of insomnia and abnormal behaviours during sleep
  - titration of PAP therapy, to determine optimal settings
  - assessment of objective response to other interventions (e.g. oral appliances for sleep apnea, positional therapy)

Home Sleep Apnea Testing
- done at home, unattended
- evaluates a limited number of parameters primarily focused on the diagnosis of OSA; EEG monitoring typically not included
- indication: evaluation for suspected OSA, in patients without significant cardiopulmonary comorbidities

OSA

Risk Factors
- obesity, craniofacial abnormalities, crowded oropharynx (including enlarged tonsils, large tongue), short/wide neck (neck circumference >17 inches (>43 cm) for men and >16 inches (>40.6 cm) for women), nasal obstruction
- more common in males than females (pre-menopause)

Signs and Symptoms
- airway obstruction: snoring, apneas, choking and gasping spells (may be witnessed by a bed partner)
- sleep fragmentation: nocturnal awakenings, nocturia, unrefreshing sleep, daytime somnolence, irritability, depression, memory loss, morning headaches

Complications
- increased risk of: hypertension, cardiovascular disease (e.g. CAD, CHF, arrhythmia), stroke, motor vehicle collisions, polycythemia, pulmonary hypertension, type 2 DM

Treatment
- modifiable factors: weight loss, decreased alcohol/sedatives, treatment of nasal congestion (usually modest effect), avoidance of supine sleep
- CPAP very effective but can be limited by compliance
- oral appliances typically less effective at reducing AHI but better tolerated by some patients
- surgical intervention can be helpful in select patients (e.g. tonsillectomy, tongue base and jaw procedures, tracheostomy
- be helpful in select patients (e.g. tonsillectomy, tongue base and jaw procedures, tracheostomy)

Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment
J Clin Sleep Med 2019;15:301-334
Purpose: To provide supporting evidence for the clinical practice guidelines for the treatment of OSA in adults using PAP.
Methods: Systematic review including 184 studies comparing use of PAP with no treatment and studies comparing different PAP modalities.
Conclusions: The data demonstrated that PAP compared to no treatment results in a clinically significant reduction in disease severity, sleepiness, blood pressure, motor vehicle accidents, and improvement in sleep-related quality of life in adults with OSA.

CSA

Risk Factors
- hypercapnic CSA: underlying disorder causing sleep hypoventilation syndrome (see *Hypoventilation Syndromes, R29*)
- non-hypercapnic CSA (mostly Cheyne-Stokes breathing): congestive heart failure, atrial fibrillation, high altitude

Signs and Symptoms
- typically those of underlying medical condition
- those with hypercapnia typically have daytime somnolence; seen less frequently in non-hypercapnic CSA

Complications
- hypercapnic CSA: may have complications of chronic hypoxemia including cor pulmonale
- hypocapnic CSA: higher mortality but not clear whether this is due to Cheyne-Stokes breathing, or if Cheyne-Stokes breathing is a marker of severe heart disease

Treatment
- both hypercapnic and non-hypercapnic CSA: treatment of underlying medical conditions, especially optimization of congestive heart failure in Cheyne-Stokes breathing
- hypercapnic CSA: typically benefit from BiPAP
- hypocapnic CSA: has not been shown to benefit from CPAP or BiPAP; clinical trials of adaptive servo-ventilation (ASV) are ongoing, but one study showed a signal for harm

Introduction to Intensive Care

Intensive Care Unit Basics

- goal is to stabilize critically ill patients: hemodynamic, respiratory, cardiac instability, or need for close monitoring

Lines and Catheters

- arterial lines
  - monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs
  - common sites: radial and femoral arteries
- central venous catheter (central line)
  - administer IV fluids, monitor CVP, insert pulmonary artery catheters
  - administer total parenteral nutrition and agents too irritating for peripheral line (e.g. vasopressors, chemotherapy)
  - common sites: internal jugular vein, subclavian vein, femoral vein
- pulmonary arterial catheter
  - balloon guides the catheter from a major vein to the right heart
  - measures PCWP via a catheter wedged in distal pulmonary artery
  - PCWP reflects the LA and LV diastolic pressure (barring pulmonary venous or mitral valve disease)
  - indications (now used infrequently due to associated complications)
    - diagnosis of shock, primary pulmonary HTN, valvular disease, intracardiac shunts, cardiac tamponade, PE
    - assessment of hemodynamic response to therapies
    - differentiation of high- vs. low-pressure pulmonary edema
    - management of complicated MI, multiorgan system failure and/or severe burns, or hemodynamic instability after cardiac surgery
  - absolute contraindications
    - tricuspid or pulmonary valve mechanical prosthesis
    - right heart mass (i.e. thrombus or tumour)
    - tricuspid or pulmonary valve endocarditis

See Landmark Respirology trials table for more information on NICE-SUGAR trial which explores the effect of intensive glucose control and mortality among adults in the ICU

Table 28. Useful Equations and Cardiopulmonary Parameters

Equations and Cardiopulmonary Parameters	
BSA = [Ht (cm) + Wt (kg) – 60]/100	PCWP = LVEDP
SV = CO / HR	SVI = CI / HR
CI = CO / BSA	RV Ejection Fraction = SV / RVEDV
SVRI = [(MAP – RAP) 80]/CI	PP = sBP – dBP
P:F ratio = PaO_2/ FiO_2	MAP = 1/3 sBP + 2/3 dBP = dBP + 1/3 PP

BSA = body surface area; CI = cardiac index; CO = cardiac output; dBP = diastolic blood pressure; HR = heart rate; LVEDP = left ventricular end diastolic pressure; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; PP = pulse pressure; RAP = right atrial pressure; RVEDV = right ventricular end diastolic volume; sBP = systolic blood pressure; SV = stroke volume; SVI = stroke volume index; SVRI = systemic vascular resistance index

Organ Failure

Table 29. Types of Organ Failure

Type of Failure	Clinical Features	Treatment
Respiratory Failure (see *Respiratory Failure* · R27)	Hypoxemia Hypercapnia	Treat underlying cause (e.g. lung disease, shunt, V/Q mismatch, drug-related, cardiac) Manage mechanical ventilation settings Supplemental oxygen
Cardiac Failure (see Cardiology and Cardiac Surgery, C40)	Hypotension Decreased urine output Altered mental status Arrhythmia Hypoxia	Treat underlying cause (e.g. myocardial ischemia, LV failure, bradycardia, tachycardia, blood loss, adrenal insufficiency) Correct volume status Vasopressors Inotropes Intra-aortic balloon pump
Coagulopathy (see Hematology, H28 and H32)	Increased INR or PTT Low platelet count Bleeding, bruising	Treat underlying cause (e.g. thrombocytopenia, drug-related, immune-related, DIC) Transfusion of blood products, clotting factors
Liver Failure (see Gastroenterology, G40)	Elevated transaminases, bilirubin Coagulopathy Jaundice Altered mental status (encephalopathy) Hypoglycemia	Treat underlying cause (e.g. viral hepatitis, drug related, metabolic) Lactulose Liver transplant
Renal Injury (see Nephrology, NP21)	Elevated creatinine Reduced urine output Signs of volume overload (e.g. CHF, effusions)	Treat underlying cause (e.g. shock, drug-related, obstruction) Correct volume and electrolyte status, eliminate toxins Diuretics Dialysis

Shock

Definition

- see Emergency Medicine, ER3
- inadequate tissue perfusion potentially resulting in end organ injury
  - categories of shock
    - hypovolemic: hemorrhage, dehydration, vomiting, diarrhea, interstitial fluid redistribution
    - cardiogenic: myopathic (myocardial ischemia ± infarction), mechanical, arrhythmic, pharmacologic
    - obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
    - distributive: sepsis, anaphylaxis, neurogenic, endocrine, toxins

Table 30. Changes Seen in Different Classes of Shock

	Hypovolemic	Cardiogenic	Obstructive	Distributive
HR	↑	↑, N, or ↓	↑	↑ or ↓
BP	↓	↓	↓	↓
JVP	↓	↑	↑	↓
Extremities	Cold	Cold	N or Cold	Warm
Other	Look for visible hemorrhage or signs of dehydration	Bilateral crackles on chest exam	Depending on cause, may see pulsus paradoxus, Kussmaul's sign, or tracheal deviation	Look for obvious signs of infection or anaphylaxis

Treatment

- treat underlying cause (hypovolemia is the most common cause)
- treatment goal is to return critical organ perfusion to normal (e.g. normalize BP)
- common treatment modalities include:
  - fluid resuscitation (NOT in cardiogenic shock)
  - inotropes (e.g. dobutamine), vasopressors (e.g. norepinephrine), vasopressin
  - revascularization or thrombolytics for ischemic events
  - needle decompression or tube thoracostomy for suspected tension pneumothorax

Causes of SHOCK

Spinal (neurogenic), Septic
Hemorrhagic
Obstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
Cardiogenic (e.g. arrhythmia, MI)
Anaphyla**K**tic

Shock: Clinical Correlation
Hypovolemic: patients have cool extremities due to peripheral vasoconstriction
Cardiogenic: patients usually have signs of left-sided heart failure
Obstructive: varied presentation
Distributive: patients have warm extremities due to peripheral vasodilation

Systemic Inflammatory Response Syndrome (SIRS): generalized inflammatory reaction caused by infectious and noninfectious entities, manifested by two or more of:

Body temperature >38°C or <36°C

Heart rate >90/min

Respiratory rate >20/min or $PaCO_2$ <32 mmHg

WBC >12000 cells/mL or <4000 cells/mL or >10% bands

Quick SOFA (qSOFA) Criteria

Respiratory rate ≥22/min

Altered mentation (GCS<15)

Systolic blood pressure ≤100 mmHg

Sepsis

- the leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- the predominant theory is that sepsis is attributable to uncontrollable immune system activation

Definitions

- sepsis: life threatening organ dysfunction caused by dysregulated host response to infection (Table 31)
- septic shock: a subset of sepsis, where sufficient circulatory and/or cellular/metabolic abnormalities substantially increase mortality. Clinically defined as sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate ≥2 mmol/L (18 mg/dL) despite adequate fluid resuscitation

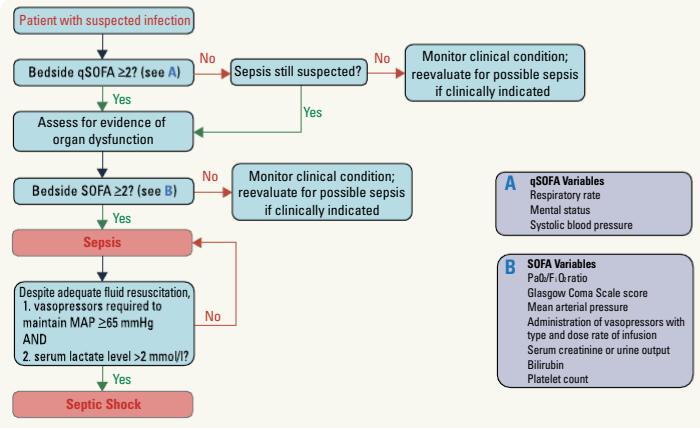
Signs and Symptoms

- new guidelines recommend the use of quick SOFA (qSOFA) criteria and SOFA score to replace SIRS criteria
- in patients with suspected infection, bedside application of qSOFA criteria identifies individuals with high likelihood of poor outcomes, including prolonged ICU stay and/or death
- a positive qSOFA (≥2 criteria) should prompt application of the SOFA score, and further evaluation of possible infection and organ dysfunction
- in the context of suspected infection, a SOFA score ≥2 reflects an overall mortality risk of 10%
- the absence of ≥2 criteria on either qSOFA or SOFA score should not delay or defer investigation or treatment of infection or any other aspect of care deemed necessary by the practitioners

Table 31. Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) Score

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiratory					
PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $x10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, µmol/L (mg/dL)	<20 (1.2)	20-32 (1.2-1.9)	33-101 (2.0-5.9)	102-204 (6.0-11.9)	>204 (12.0)
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5a or dobutamine (any dose)[a]	Dopamine 5.1-15 [a]or epinephrine <0.1 [a]or norepinephrine <0.1[a]	Dopamine >15 [a]or epinephrine >0.1[a] or norepinephrine >0.1[a]
Central Nervous System					
Glasgow coma scale score	15	13-14	10-12	6-9	<6
Renal					
Creatinine, µmol/L (mg/dL)	<110 (1.2)	110-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9)	>440 (5.0)
Urine output, mL/d				<500	<200

[a]Catecholamine doses are given as µg/kg/min for at least 1hr
Table adapted from Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-810



The baseline Sequential (sepsis-related) Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have pre-existing (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicated quick SOFA; MAP, mean arterial pressure.

Figure 11. Approach to sepsis
Figure adapted from Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-810

Treatment

- identify the cause and source of infection: blood, sputum, urine Gram stain, and C&S
- initiate empiric antibiotic therapy
- monitor, restore, and maintain hemodynamic function

Surviving Sepsis

Adapted from International Guidelines for Management of Severe Sepsis and Septic Shock 2012

- adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with demand
- initial resuscitation (goal during first 6 h of resuscitation for sepsis induced hypotension persisting after initial fluid challenge or blood lactate ≥4 mmol/L)
- maintain CVP 8-12 mmHg with IV crystalloids/colloids
  - maintain MAP ≥65 mmHg with use of vasopressor agents, first line: norepinephrine
  - urine output ≥0.5 mL/kg/h
  - central venous (SVC) or mixed oxygen saturation 70% or 65%, respectively
  - in patients with elevated lactate levels target resuscitation to normalize lactate
  - corticosteroid replacement therapy not indicated if adequate hemodynamic stability achieved with fluid resuscitation and vasopressor therapy

- infection control
  - prompt diagnosis of infection
    - cultures as clinically indicated prior to antibiotic therapy if no significant delay
    - imaging studies performed promptly to confirm possible infectious source
  - antibiotic therapy
- administer effective IV antimicrobials within first hour of recognition of sepsis
  - choice of anti-infective therapy should consider activity against all likely pathogens and penetrance of adequate concentration into tissue presumed to be source of infection
  - antimicrobial regimen should be reassessed daily for potential de-escalation
- surgical source control when appropriate
- supportive oxygenation and ventilation using lung-protective regimen
- early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier
- DVT/PE prophylaxis
- advanced care planning, including the communication of likely outcome and realistic goals of treatment with patients and families

See Landmark Respirology trials table for more information on ARISE trial which assessed the effect of early goal-directed therapy compared to usual care on the mortality of early septic shock patients in the emergency department

Common Medications

Table 32. Common Medications for Respiratory Diseases

	Drug	Typical Adult Dose	Indications	Side Effects
β2-AGONISTS				
Short-Acting β2-Agonists	salbutamol/albuterol (Ventolin®, Airomir®) (light blue/navy MDI or diskus) terbutaline (Bricanyl®) (blue turbuhaler)	1-2 puffs q4-6 h PRN	Rescue bronchodilator used in COPD and asthma	CV (angina, flushing, palpitations, tachycardia, can precipitate atrial fibrillation), CNS (dizziness, H/A, insomnia, anxiety), GI (diarrhea, N/V), rash, hypokalemia
Long-Acting β2-Agonists	salmeterol (Serevent®) (green diskus), formoterol (Oxeze®, Foradil®) (blue/green turbuhaler or aerolizer), indacaterol (Onbrez®) (blue/white breezhaler)	1 puff BID 1-2 puffs BID 1 puff daily	Maintenance bronchodilator used in COPD	
Combination Long-Acting β2-Agonist and Inhaled Corticosteroid	fluticasone and salmeterol (Advair®, Wixela®) (purple MDI or diskus or Inhub®), budesonide and formoterol (Symbicort®) (red turbuhaler), mometasone and formoterol (Zenhale®) (blue MDI) fluticasone furoate and Vilanterol (Breo Ellipta®) (light gray and blue inhaler) Mometasone and indacaterol (Atectura®) (white Breezhaler®)	1 puff BID (diskus/Inhub) 2 puffs bid (MDI) 1-2 puffs BID 2 puffs BID 1 puff daily	Maintenance bronchodilator/ anti-inflammatory used in COPD and asthma	Common: CNS, H/A, dizziness Resp: URTI, GI (N/V, diarrhea, pain/discomfort, oral candidiasis)
Combination Short-Acting β2-Agonist and Short-Acting Anti-Cholinergic	ipratropium/salbutamol (Combivent®, Respimat®) (orange respimat)	1 puff QID	Rescue bronchodilator used in COPD	Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs
Combination Long-Acting β2-Agonist and Long-Acting Anti-Cholinergic	umeclidinium/vilanterol (Anoro®) (red ellipta) aclidinium/formoterol (Duaklir®) (yellow genuair) tiotropium/olodaterol (Inspiolto®) (green respimat) indacaterol/glycopyrronium (Ultibro®) (yellow breezhaler)	1 puff daily 1 puff BID 2 puffs daily 1 puff daily	Maintenance bronchodilator used in COPD	Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs
ANTICHOLINERGICS				
Short-Acting Anti-Cholinergic	ipratropium bromide (Atrovent®) (clear/green MDI)	2-3 puffs QID	Rescue bronchodilator used in COPD and asthma	Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs
Long-Acting Anti-Cholinergic	tiotropium bromide (Spiriva®) (green handihaler or respimat), glycopyrronium bromide (Seebri®) (orange breezhaler), umeclidinium (Incruse™) (green ellipta), aclidinium (Tudorza®) (green Genuair®)	1 puff QAM 1 puff daily	Maintenance bronchodilator used in COPD and asthma	Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs
CORTICOSTEROIDS				
Inhaled	fluticasone (Flovent®) (orange/peach MDI or diskus) budesonide (Pulmicort®) (brown turbuhaler) ciclesonide (Alvesco®) (red MDI) beclomethasone (QVAR®) (brown MDI) mometasone (Asmanex®) (pink/grey/brown twisthaler) fluticasone furoate (Arnuity®) (orange ellipta) futicasone propionate (Aermony RespiClick®) (white and green inhaler)	1-4 puffs BID 1-2 puffs BID 1 -2 puffs daily or BID 1-4 puffs BID 1 puff daily or BID 1 puff daily 1 puff BID	Maintenance anti-inflammatory used in asthma	H/A, fever, N/V, MSK pain, URTI, throat irritation, growth velocity reduction in children/adolescents, HPA axis suppression, increased pneumonia risk in COPD
Systemic	prednisone (Apo-prednisone®, Deltasone®) methylprednisolone (Depo-Medrol®, Solu-Medrol®)	Typically 40-60 mg/d PO Typically 125 mg q8 h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q6 h for 5 d	Acute exacerbation of COPD; severe, persistent asthma, *Pneumocystis carinii* pneumonia Status asthmaticus	Endocrine (hirsutism, DM/glucose intolerance, Cushing's syndrome, HPA axis suppression), GI (increased appetite, indigestion), ocular (cataracts, glaucoma), edema, avascular necrosis, osteoporosis, H/A, psychiatric (anxiety, insomnia), easy bruising

See Infectious Diseases, ID25 for the management of pulmonary tuberculosis

Table 32. Common Medications for Respiratory Diseases

	Drug	Typical Adult Dose	Indications	Side Effects
ADJUNCT AGENTS				
	theophylline (Uniphyll®)	400-600 mg once daily	Treatment of symptoms of reversible airway obstruction due to COPD	GI upset, diarrhea, N/V, anxiety, H/A, insomnia, muscle cramp, tremor, tachycardia, premature ventricular contractions, arrhythmias Toxicity: persistent, repetitive vomiting, seizures
LEUKOTRIENE ANTAGONISTS				
	omalizumab (Xolair®)	150-375 mg SC q2-4 wk	Moderate-severe persistent asthma	H/A, sinusitis, pharyngitis, URTI, viral infection, thrombocytopenia, anaphylaxis
PDE-4 INHIBITORS				
	roflumilast (Daxas®)	500 µg PO once daily	Chronic bronchitis with frequent exacerbations	Weight loss, suicidal ideation
ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA				
Macrolide	erythromycin	250-500 mg PO TID x 7-10 d	Alternate to doxycycline or fluoroquinolone	GI (abdominal pain, diarrhea, N/V), H/A, prolonged QT, ventricular arrhythmias, hepatic impairment
	azithromycin	500 mg PO x 1 dose, then 250 mg once daily x 4		GI (diarrhea, N/V, abdominal pain), renal failure, deafness
	clarithromycin	1000 mg once daily or 500 mg PO BID x 7-10 d		H/A, rash, GI (diarrhea, N/V, abnormal taste, heartburn, abdominal pain), increased urea
Doxycycline		100 mg PO BID x 7-10 d	Alternate to macrolide or fluoroquinolone	Photosensitivity, rash, urticaria, anaphylaxis, diarrhea, enterocolitis, tooth discolouration in children
Fluoroquinolone	levofloxacin (Levaquin®)	500 mg PO once daily x 7-10 d or 750 mg PO once daily x 5 d	Alternate to macrolide or doxycycline	CNS (dizziness, fever, H/A), GI (N/V, diarrhea, constipation), prolonged QT
	moxifloxacin (Avelox®)	400 mg PO once daily x 7 d		
ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA				
4th gen Cephalosporin with MSSA activity	cefepime	1-2 g IV once daily x 7-10 d	Combine with fluoroquinolone or macrolide	Rash, diarrhea, eosinophilia, thrombocytosis, leukopenia, elevated transaminases
Fluoroquinolone	levofloxacin moxifloxacin	750 mg PO once daily x 5 d 400 mg PO once daily x 7 d (5 d for AECOPD)	Combine with 3rd gen cephalosporin	Rash, diarrhea, eosinophilia, thrombocytosis, leukopenia, elevated transaminases
Piperacillin/Tazobactam (Tazocin®), imipenem or meropenem	Piperacillin/Tazobactam	4.5 g IV q6-8 h x 7-10 d	Suspect *Pseudomonas*	CNS (confusion, convulsions, drowsiness), rash, hematologic (abnormal platelet aggregation, prolonged PT, positive Coombs)
	imipenem	500 mg IV q6h x 7d		
	meropenem	1 g IV q8h x 7d		
Vancomycin (Vancocin®)		1 g IV BID x 7-10 d	Suspect MRSA	CNS (chills, drug fever), hematologic (eosinophilia), rash, red man syndrome, interstitial nephritis, renal failure, ototoxicity
Macrolide	azithromycin	500 mg IV once daily x 2 d, then 500 mg PO once daily x 5 d	Suspect *Legionella*	CNS (chills, drug fever), hematologic (eosinophilia), rash, red man syndrome, interstitial nephritis, renal failure, ototoxicity
	clarithromycin	1000 mg once daily or 500 mg PO BID x 7-10 d		
ICU MEDICATIONS				
Pressors/Inotropes	norepinephrine (Levophed®) phenylephrine dobutamine	0.5-30 µg/min IV 0.5 µg/kg/min IV 2-20 µg/kg/min IV	Acute hypotension Severe hypotension Inotropic support	Angina, bradycardia, dyspnea, hyper/hypotension, arrhythmias
Sedatives/Analgesia	fentanyl (opioid class)	50-100 µg then 50-unlimited µg/h IV	Sedation and/or analgesia	Bradycardia, respiratory depression, drowsiness, hypotension
	propofol (anesthetic)	1-3 mg/kg then 0.3-5 mg/kg/h IV	Sedation	Apnea, bradycardia, hypotension (good for ventilator sedation)

See Infectious Diseases, ID25 for the management of pulmonary tuberculosis

Landmark Respirology Trials

Trial Name	Reference	Clinical Trial Details
ACUTE RESPIRATORY DISTRESS SYNDROME		
ARDS Network	NEJM 2000;342:1301-08	**Title:** Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome **Purpose**: Determine whether ventilation with lower tidal volumes would improve clinical outcomes in ARDS patients. **Methods**: Patients with ALI and ARDS were randomized to traditional ventilation treatment (12 mL/kg) or a lower tidal-volume ventilation strategy (6 mL/kg). The primary outcome was death before patient discharge. **Results**: Mortality was lower in patients treated with lower tidal volumes (31.0% vs. 39.8%; P=0.007), and the number of days without ventilation use was greater in this group (P=0.007). **Conclusions**: Both all-cause mortality and days with ventilator use were decreased in ARDS patients ventilated with a low tidal volume strategy.
ACURASYS	NEJM 2010;363:1107-16	**Title:** Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome **Purpose**: Evaluate clinical outcomes after 2 d of therapy with neuromuscular blocking agents, in patients with ARDS. **Methods**: 340 patients presenting to the ICU with severe ARDS were randomized to cisatracurium besylate or placebo. The primary outcome was the proportion of patients who died before hospital discharge. **Results**: The hazard ratio for 90 d mortality was 0.68 (95% CI 0.48 to 0.98; P=0.04). The crude 90 d mortality was 31.6% in the intervention group and 40.7% in the placebo group. The rates of ICU-acquired paresis did not differ between groups. **Conclusions**: Early administration of a neuromuscular blocking agent in patients with severe ARDS improved 90-d survival and reduced time on a ventilator.
OSCILLATE	NEJM 2013;368:795-805	**Title:** High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome **Purpose**: Assess the reduction in mortality conferred by high-frequency oscillatory ventilation (HFOV) among adults with ARDS. **Methods**: Adults with new-onset moderate-severe ARDS were randomized to HFOV or a control ventilation strategy. The primary outcome was all-cause in-hospital mortality. **Results**: In-hospital mortality was 47% in the HFOV group and 35% in the control group (RR 1.33; 95% CI 1.09 to 1.64; P=0.005). Patients in the HFOV group received higher doses of midazolam (P<0.01) and vasoactive drugs (91% vs. 84%; P=0.01) than control patients. **Conclusions**: Early HFOV in patients with moderate-to-severe ARDS may increase in-hospital mortality.
PROSEVA	NEJM 2013;368:2159-68	**Title:** Prone Positioning in Severe Acute Respiratory Distress Syndrome **Purpose**: Evaluate the effect of early application of prone positioning on patients with severe ARDS. **Methods**: 466 patients with severe ARDS were randomized to undergo prone-positioning sessions >16 h or remain supine. The primary outcome was the proportion of patients who died from any cause at 28 d. **Results**: The 28 d mortality was 16.0% in the prone group and 32.8% in the supine group (hazard ratio 0.39; 95% CI 0.25 to 0.63; P<0.001). Unadjusted 90 d mortality was 23.6% in the prone group and 41.0% in the supine group (hazard ratio 0.44; 95% CI 0.29 to 0.67; P<0.001). The incidence of complications did not differ significantly between groups. **Conclusions**: Early application of prolonged prone-positioning sessions in patients with severe ARDS decreased 28 d and 90 d mortality.
ASTHMA		
SMART	Chest 2006; 129:15-26	**Title:** The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy plus Salmeterol **Purpose**: Compare the safety of salmeterol xinafoate or placebo, when added to the usual asthma treatment regimen. **Methods**: Subjects with asthma without a history of LABA use were randomized to salmeterol 42 mg BID, or placebo BID via MDI. Results: The occurrence of the primary outcome, respiratory related deaths, or life-threatening experiences were not significantly different between salmeterol and placebo (50 vs. 36; RR 1.40; 95% CI 1.25 to 15.34). Subgroup analyses suggest that there is increased risk in African Americans compared with Caucasian subjects. **Conclusions**: Salmeterol added to usual asthma care increases the risk of respiratory-related and asthma-related deaths, particularly among African American patients reporting no baseline use of ICS.
EXTRA	Ann Intern Med 2011;154:573-82	**Title:** Omalizumab in Severe Allergic Asthma Inadequately Controlled with Standard Therapy **Purpose**: Evaluate the safety and efficacy of omalizumab in inadequately controlled severe asthma, without additional inhaler therapy. **Methods**: 850 patients with inadequately controlled asthma despite high-dose ICS plus LABAs were randomized to omalizumab or placebo for 48 wk. The primary endpoint was the rate of exacerbations over the study period. **Results**: The rate of protocol-defined asthma exacerbations were lower in omalizumab-treated patients than control patients (0.66% vs. 0.88%; P=0.006). The incidence of adverse events and serious adverse events were similar between groups. **Conclusions**: Addition of omalizumab in patients with uncontrolled severe allergic asthma reduces exacerbations and provides additional clinical benefits.
PATHWAY	NEJM 2017;377:936-46	**Title:** Tezepelumab in Adults with Uncontrolled Asthma **Purpose**: Evaluate the safety and efficacy of Tezepelumab, in patients with uncontrolled asthma despite LABA and medium-high ICS dose. **Methods**: Patients were randomized to Tezepelumab at three dose levels versus placebo over a 52-wk period. The primary endpoint was the annualized rate of asthma exacerbations. **Results**: Exacerbation rates in the Tezepelumab groups were lower by 62%, 71% and 66% than in the placebo group (P<0.001 for all comparisons). **Conclusions**: Among patients treated with LABA and medium-high doses of ICS, those who received Tezepelumab had lower rates of clinically significant asthma exacerbations than those who received placebo.
Novel START	NEJM 2019;380:2020-30	**Title:** Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma **Purpose**: Determine the efficacy of budesonide-formoterol versus SABAs in reducing asthma exacerbations. **Methods**: Patients with mild asthma were randomized to albuterol 100 µg, budesonide 200 µg plus albuterol prn, or budesonide-formoterol prn. The primary outcome was the annualized rate of asthma exacerbations. **Results**: The annualized exacerbation rate was lower in the combination group than in the albuterol group (0.195 vs. 0.400; RR 0.49; 95% CI 0.33 to 0.72; P<0.01). This did not differ significantly in the budesonide maintenance group (RR 1.12; 95% CI 0.70 to 1.79; P=0.65). The incidence of adverse events was consistent with previous trials. **Conclusions**: For the prevention of asthma exacerbations, budesonide-formoterol prn was superior to albuterol prn and did not differ significantly from budesonide maintenance.

Trial Name	Reference	Clinical Trial Details
PrimoTinA-asthma 1 and PrimoTinA-asthma 2	NEJM 2021;367:1198-1207	**Title:** Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy **Purpose**: Determine the efficacy and safety of adding tiotropium bromide to a LABA and ICS combination treatment in the context of asthma. **Methods**: 912 adult patients from two randomized double-blind controlled trials were analyzed in the study. These participants, on LABA and ICS combination therapy, were randomly assigned to either the tiotropium or placebo group. Primary endpoint was FEV1 response and prevention of severe exacerbations. **Results**: The use of tiotropium resulted in better primary outcomes compared to placebo group as assessed by adjusted peak FEV1 (difference of 86mL; P=0.01 in trial 1 and 154mL; P<0.001 in trial 2) and time to first severe exacerbation (difference of 56 d). **Conclusions**: Tiotropium improved lung function and delayed severe exacerbations in patients with uncontrolled asthma when added to LABA and ICS treatment regimen.
CHRONIC OBSTRUCTIVE PULMONARY DISEASE		
TORCH	NEJM 2007;356:775-89	**Title:** Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease **Purpose**: Analyze the survival benefits of LABA and ICS in COPD patients. **Methods**: Patients with COPD were randomized to salmeterol 50 µg plus fluticasone propionate 500 µg BID, administered with a single placebo inhaler, salmeterol alone or fluticasone alone. The primary outcomes were all-cause mortality and the frequency of exacerbations. **Results**: All-cause mortality rates were 12.6% in the combination group, 15.2% in the placebo group, 13.5% in the salmeterol group and 16.0% in the fluticasone group (hazard ratio combination vs. placebo 0.825; 95% CI 0.681 to 1.002; P-0.052). Mortality in the salmeterol or fluticasone monotherapy group did not differ from placebo. **Conclusions**: Combination of ICS and LABAs improves COPD symptoms, reduces exacerbations, and shows a trend to lower mortality.
UPLIFT	NEJM 2008;359:1543-54	**Title:** A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease **Purpose**: Examine the long-term effects of tiotropium therapy in patients with COPD. **Methods**: Patients with COPD, permitted to use all drugs except LAACs, were randomized to 4 yr of tiotropium or placebo. The primary endpoints were the rate of decline in FEV1 before and after bronchodilation. **Results**: Mean differences in FEV1 were maintained throughout the trial between the tiotropium and placebo groups (87-103 mL before bronchodilation; 47-65 mL after bronchodilation). The 30 d differences between groups were not significant. **Conclusions**: Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect FEV1 decline.
ROFLUMILAST	Lancet 2009;374:695-703	**Title:** Roflumilast in Moderate-to-severe Chronic Obstructive Pulmonary Disease Treated with Long Acting Bronchodilators **Purpose**: Investigate the effect of phosphodiesterase-4 (PDE4) inhibitor roflumilast on lung function in COPD patients treated with salmeterol or tiotropium. **Methods**: Patients >40 yr with moderate-severe COPD were randomized to oral roflumilast 500 µg or placebo OD for 24 wk, in addition to salmeterol or tiotropium. The primary endpoint was a change in prebronchodilator FEV1. **Results**: Compared with placebo, treatment with roflumilast improved mean FEV1 by 49 mL (p<0.0001) in patients treated with salmeterol, and 80 mL (0.0001) in patients treated with tiotropium. Roflumilast had benefits on other measures of lung function in both groups. **Conclusions**: PDE4 inhibitor roflumilast improves FEV1 when used as add-on therapy in COPD patients on tiotropium or salmeterol.
POET-COPD	NEJM 2011;364:1093-103	**Title:** Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD **Purpose**: Investigate whether the LAAC tiotropium is superior to the LABA salmeterol in preventing COPD exacerbations. **Methods**: Patients with moderate-severe COPD and a history of exacerbations were randomized to tiotropium 18 µg OD or salmeterol 50 µg BID. The primary outcome was time to the first exacerbation during the study period. **Results**: Tiotropium, as compared with salmeterol, increased the time to first exacerbation, with a 17% risk reduction (hazard ratio 0.83; 95% CI 0.77 to 0.90; P<0.001). Tiotropium also reduced the number of moderate and severe exacerbations (0.64 vs. 0.72; rate ratio 0.89; 95% CI 0.83 to 0.96; P=0.002). **Conclusions**: Tiotropium decreases the number of moderate-to-severe COPD exacerbations in comparison to salmeterol.
REDUCE	JAMA 2013;309:2223-31	**Title:** Short-term vs. Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease **Purpose**: To investigate whether a short-term systemic steroid treatment is noninferior to conventional treatment. **Methods**: 314 patients presenting to the ED with acute COPD exacerbations were randomized to prednisone 40 mg for either 5 (short-term) or 14 (conventional) d. The primary endpoint was the time for the next exacerbation in 180 d. **Results**: In the intention-to-treat analysis, hazard ratios between groups were 0.95 (95% CI 0.70 to 1.29; P=0.006). In the short-term group, 35.9% of patients reached the endpoint while 36.8% patients in the conventional group reached the endpoint. There was no difference between groups in time to death or recovery of lung function. **Conclusions**: A 5-d course of glucocorticoids is non-inferior to a 14-d course for treatment of acute COPD exacerbations.
FLAME	NEJM 2016;374:2222-34	**Title:** Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD **Purpose**: Elucidate the role of a LAMA-LABA treatment regimen in COPD patients with a high risk of exacerbations. **Methods**: Patients with COPD and a history of >1 exacerbation in the prior year were randomized to incadeterol 100 µg plus glycopyrronium 50 µg, or salmeterol 50 µg plus fluticasone 500 µg. The primary outcome was the annual rate of all COPD exacerbations. **Results**: The rate of exacerbations was 11% lower in the indacaterol-glycopyrronium group relative the salmeterol-fluticasone group (3.59 vs. 4.03; rate ratio 0.89; 95% CI 0.83 to 0.96; P=0.003). The annual rate of moderate-severe exacerbations was lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (0.98 vs. 1.19; rate ratio 0.83; 95% CI 0.75 to 0.91; P<0.001). **Conclusions**: LABA+LAMA regimen of indacaterol-glycopyrronium was more effective than a LABA+ICS regimen of salmeterol-fluticasone in preventing COPD exacerbations.
IMPACT	NEJM 2018;378:1671-80	**Title:** Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD **Purpose**: Assess the benefits of triple-therapy with ICS, LAMA and LABA, compared with dual therapy in COPD patients. **Methods**: 10355 patients with COPD were randomized to fluticasone-umeclidinium-vilanterol, fluticasone furoate-vilanterol or umeclidinium-vilanterol. The primary outcome was the annual rate of moderate-severe COPD exacerbations. **Results**: The rate of exacerbations was 0.91 per yr in the triple therapy group, compared with 1.07 per yr with fluticasone furoate-vilanterol group and 1.21 per yr in the umeclidinium-vilanterol group (rate ratio with triple-therapy 0.75; 95% CI 0.70 to 0.81; P<0.001). The annual rate of hospitalizations was 0.18 in the triple-therapy group compared with 0.19 in the umeclidinium-vilanterol group (rate ratio 0.66; 95% CI 0.56 to 0.78; P<0.001). **Conclusions**: Triple therapy with an ICS+LAMA+LABA resulted in a lower rate of moderate or severe COPD exacerbations than dual therapy.

Trial Name	Reference	Clinical Trial Details
INTERSTITIAL LUNG DISEASE		
PANTHER	NEJM 2012; 366:1968-1977	**Title:** Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis **Purpose**: To evaluate the safety and efficacy of a three drug regimen (prednisone, azathioprine and N-acetylcysteine(NAC)) for IPF. **Methods**: Patients with mild to moderate IPF were randomized to the active drug combination, NAC alone or placebo. The primary endpoint was change in FVC. **Results**: The trial was terminated early when an interim analysis demonstrated that patients in the active drug combination arm had an increased rate of death (8 vs. 1) and hospitalization (23 vs. 7) when compared to placebo. No evidence of benefit was identified in any physiological measurements such as FVC. **Conclusions**: Patients with IPF treated with prednisone, azathioprine and NAC had increased risk of death and hospitalization when compared to no treatment.
INPULSIS	NEJM 2014;370:2071-82	**Title:** Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis **Purpose**: Evaluate the safety and efficacy of Nintedanib in patients with IPF. **Methods**: Patients with IPF were randomized to Nintedanib 150 mg twice daily or placebo. The primary endpoint was the annual rate of decline in FVC. **Results**: The annual rate of change in FVC was -114.7 mL with Nintedanib versus -239.9 mL with placebo (difference 125.3 mL; 95% CI 77.7 to 172.8; P<0.001) in INPULSIS-1. In INPULSIS-2, the same metric was -113.6 mL with Nintedanib versus -207.3 mL with placebo (difference 93.7 mL; 95% CI 44.8 to 142.7; P<0.001). There was a reduction in acute exacerbations of IPF in the treatment arms but no mortality difference. **Conclusions**: Nintedanib reduces the decline in FVC in patients with IPF.
ASCEND	NEJM 2014;370:2083-92	**Title:** A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis **Purpose**: Confirm the beneficial effects of pirfenidone on disease progression in patients with IPF. **Methods**: 555 patients with IPF were randomized to oral pirfenidone (2403 mg daily) or placebo for 52 wk. The primary endpoint was change in FVC or death at the study period. **Results**: There was a relative reduction of 47.9% in the proportion of patients with 10% decline in FVC, in the pirfenidone group compared to placebo (P<0.001). Pirfenidone improved progression-free survival (P<0.001). There was no significant difference in dyspnea scores (P=0.16), all-cause mortality (0.10) or IPF mortality (P=0.23) between groups. In a pooled analysis with prior trials, there was a reduction in mortality. **Conclusions**: Pirfenidone reduces disease progression in patients with IPF.
INBUILD	NEJM 2019; 381:1718-1727	**Title:** Nintedanib in Progressive Fibrosing Interstitial Lung Diseases **Purpose**: Evaluate the efficacy of Nintedanib across a broad range of progressive fibrosing lung diseases. **Methods**: Patients with significant, progressive fibrosing lung disease of any cause were randomized to Nintedanib 150 mg twice daily or placebo. The primary endpoint was the annual rate of decline in FVC. **Results**: 663 patients treated. The average annual rate of change in FVC was -80.8 mL in the Nintedanib group and -187.8 mL in the placebo group. Patients with UIP type pattern on imaging had a difference of -82.9 mL versus -211.1 mL favouring Nintedanib. **Conclusions**: In patients with progressive fibrosing interstitial lung diseases, Nintedanib reduced the annual rate of decline in FVC.
PULMONARY EMBOLISM		
EINSTEIN-PE	NEJM 2012;366:1287-97	**Title:** Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism **Purpose**: Assess the effectiveness of fixed-dose rivaroxaban for the treatment of deep vein thrombosis (DVT). **Methods**: 4832 patients with acute symptomatic PE with-or-without DVT were randomized to rivaroxaban 15 mg BID or to standard therapy with enoxaparin followed by a vitamin-K antagonist. The primary outcome was symptomatic recurrent VTE. **Results**: Rivaroxaban was noninferior to standard therapy (P=0.003) for the primary outcome, with 2.1% and 1.8% event rates in the rivaroxaban and standard-therapy groups, respectively (hazard ratio 1.12; 95% CI 0.75 to 1.68). Major or non-major clinically relevant bleeding occurred in 10.3% of rivaroxaban-treated patients and 11.4% of patients receiving standard therapy (hazard ratio 0.90; 95% CI 0.76 to 1.07; P=0.23). **Conclusions**: Fixed dose of rivaroxaban was non-inferior to standard therapy (Vitamin K antagonist) for the initial and long-term treatment of PE.
EPSTEIN-CHOICE	NEJM 2017;376:1211-22	**Title:** Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism (EPSTEIN CHOICE) **Purpose**: To assess the efficacy of full- or lower-intensity anticoagulation therapy in the extended treatment of VTE. **Methods**: 3396 patients with VTE were randomized to receive either rivaroxaban 10 or 20 mg once daily, or 100 mg of ASA. All study patients had completed 6 to 12 mo of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal VTE, and the principal safety outcome was major bleeding. **Results**: The primary efficacy outcome occurred in 17 of 1107 patients (1.2%) receiving rivaroxaban, compared to 50 of 1131 patients (4.4%) receiving ASA (hazard ratio for 20 mg rivaroxaban vs. ASA 0.34; 95% CI 0.20 to 0.59; hazard ratio for 10 mg rivaroxaban vs. ASA 0.26; 95% CI 0.14 to 0.47; P<0.001 for all comparisons). The incidence of adverse events, including major and nonmajor clinically relevant bleeding, were similar among all groups. **Conclusions**: Among patients with VTE in equipoise for continued anticoagulation, the risk of a recurrent event was lower with rivaroxaban (10 or 20 mg) than with ASA, without a significant increased risk of adverse events.
OBSTRUCTIVE SLEEP APNEA		
CPAP and Central Sleep Apnea	NEJM 2005;353:2025-33	**Title:** Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure **Purpose**: Test the effectiveness of CPAP on survival outcomes without heart transplantation, in patients with CHF and CSA. **Methods**: 258 patients with HF and CSA were randomized to CPAP or no-CPAP. Sleep studies were conducted, and the primary outcomes were ejection fraction (EF), exercise capacity and quality of life. **Results**: The CPAP group had greater reductions in the frequency of apneic episodes, greater increases in mean nocturnal O_2 sat (1.6% vs. 0.4%; P<0.001) and EF (2.2% vs. 0.4; P=0.02). There were no differences in the number of hospitalizations or quality of life. **Conclusions**: CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF.
SAVE	NEJM 2016;375:919-31	**Title:** CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea **Purpose**: To determine whether CPAP reduces cardiovascular events in patients with sleep apnea. **Methods**: 2687 participants recruited from 7 different countries were randomly assigned to receive either standard care or CPAP with standard care. Primary endpoints measured were death from cardiovascular cause, MI, stroke, or hospitalizations for CHF, acute coronary syndrome, or TIA. **Results**: There was no significant difference between the CPAP + standard care group and the standard care group in terms of cardiac events (HR 1.10, P=0.34). **Conclusions**: CPAP does not reduce the risk of cardiovascular events in patients with OSA.

Trial Name	Reference	Clinical Trial Details
INTENSIVE CARE		
NICE-SUGAR	NEJM 2009;360:1283-1297	**Title**: Intensive versus Conventional Glucose Control in Critically Ill Patients **Purpose**: To determine the optimal target range for blood glucose in critically ill patients. **Methods**: 6104 patients admitted to the intensive care unit (ICU) were randomized to receive either intensive control or conventional control of glucose control. Primary endpoints were measured as death from any cause within 90 d after randomization. **Results**: The odds ratio for death in the intensive control group was 1.14 (95% CI 1.02-1.28; P=0.02) and this effect did not differ between surgical and medical patients. A blood glucose target of 180 mg or less per dL resulted in lower mortality compared to a target of 81 to 108 mg per dL Conclusions: Intensive glucose control increased mortality among adults in the ICU.
ARISE	NEJM 2014; 371:1496-1506	**Title**: Goal-Directed Resuscitation for Patients with Early Septic Shock **Purpose**: To determine whether Early goal-directed therapy (EGDT) reduces all-cause mortality. **Methods**: 1600 patients presenting to the emergency department with early septic shock were randomly assigned to receive either EGDT or usual care. **Results**: Mortality did not differ between patients treated with EGDT or usual care (absolute risk difference EGDT vs. usual care = -0.3%, 95% CI -4.1 to 3.6%; P=0.90). Conclusions: EGDT did not reduce all-cause mortality in critically ill patients presenting to the emergency department.

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RH Rheumatology

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Acronyms

AAV	antineutrophil cytoplasmic antibody-associated vasculitis
Ab	antibody
ACPA	anti-citrullinated protein antibodies
Ag	antigen
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
Anti-RNP	antiribonuclear protein
Anti-Sm	anti-Smith antibodies
Anti-SRP	anti-signal recognition particle
Anti-SSA	anti-Sjögren's-syndrome-related antigen A
APLA	antiphospholipid antibodies
APS	antiphospholipid antibody syndrome
aPTT	activated partial thromboplastin time
AS	ankylosing spondylitis
AVN	avascular necrosis
BlyS	B-lymphocyte stimulator
CCB	calcium channel blocker
CCP	cyclic citrullinated peptide
CK	creatine kinase
CMC	carpometacarpal joint
CNS	central nervous system
CTD	connective tissue disease
CPPD	calcium pyrophosphate deposition disease
CRP	C-reactive protein
CVA	cerebrovascular accident
CVS	cardiovascular system
DAT	direct antiglobulin test
DEXA	dual energy x-ray absorptiometry
DIP	distal interphalangeal joint
DMARD	disease-modifying anti-rheumatic drug
DMM	dermatomyositis
dsDNA	double stranded DNA
EA	enteropathic arthritis
ECASA	enteric-coated acetylsalicylic acid
EGPA	eosinophilic granulomatosis and polyangiitis
FVC	forced vital capacity
GC	Neisseria gonorrhoeae gonococcus
GCA	giant cell arteritis
GPA	granulomatosis with polyangiitis
H/A	headache
HLA	human leukocyte antigen
IA	intra-articular
IBD	inflammatory bowel disease
IBM	inclusion body myositis
IE	infective endocarditis
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
ILD	interstitial lung disease
IP	interphalangeal joint
ITP	idiopathic thrombocytopenic purpura
MCP	metacarpophalangeal joint
MCTD	mixed connective tissue disease
MHC	major histocompatibility complex
MPA	microangiopathic polyangiitis
MPO	myeloperoxidase
MTP	metatarsophalangeal joint
MTX	methotrexate
NAM	necrotizing autoimmune myositis
OA	osteoarthritis
PAN	polyarteritis nodosa
PIP	proximal interphalangeal joint
PM	polymyositis
PMN	polymorphonuclear leukocyte
PMR	polymyalgia rheumatica
PR3	proteinase 3
PsA	psoriatic arthritis
PTT	partial thromboplastin time
PUD	peptic ulcer disease
RA	rheumatoid arthritis
ReA	reactive arthritis
RF	rheumatoid factor
ROM	range of motion
SI	sacroiliac
SNRI	serotonin-norepinephrine reuptake inhibitors
SpA	spondyloarthritis
SS	Sjögren's syndrome
SSA	Sjögren's syndrome antigen A
SSB	Sjögren's syndrome antigen B
SSc	systemic sclerosis
SSZ	sulfasalazine
TNF	tumour necrosis factor
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
U-SpA	undifferentiated spondyloarthropathy

Anatomy of Joint Pathology

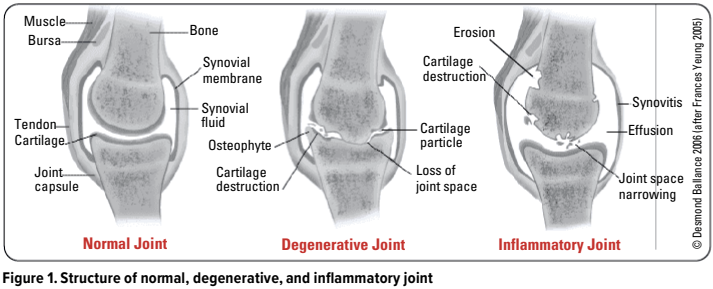

Figure 1. Structure of normal, degenerative, and inflammatory joint

Terminology in Rheumatology

Arthritis: inflammation in the joint(s)
- Joint swelling: effusion/synovial thickening
- Pain
- Warmth
- Erythema

Arthralgia: joint pain without swelling, redness, or warmth

Innate Immune Cells
Neutrophil (PMN): circulates in blood and responds to inflammatory stimuli, kills invading organisms by phagocytosis, degranulation, and neutrophil extracellular traps
Natural Killer Cell: innate immunity against intracellular infections (especially viruses), killing function, and produces cytokines
Macrophage: arrives after PMNs, suppresses PMN efflux and phagocytoses PMN debris, secretes pro-inflammatory cytokines in response to microbial debris
Dendritic Cell: actively phagocytic when immature, activated by signals from toll-like receptor (TLR), releases pro-inflammatory cytokines, presents antigens to T cells in lymph nodes
Eosinophil: responds to inflammatory cytokines and degranulates, releasing reactive oxygen species and cytokines, associated with allergy, asthma, and parasitic infection
Mast Cell: presents in connective tissue and mucosa, allergen cross-linking of IgE bound to mast cell triggers degranulation and the release of inflammatory mediators

Basics of Immunology

Immune Mechanisms of Disease

Table 1. Mechanisms of Immune-Mediated Disorders

Type	Pathophysiology	Examples
IgE-Mediated/Immediate Hypersensitivity (Type I)	Allergens bind to IgE antibodies on mast cells, inducing their degranulation	Asthma, allergic rhinitis, anaphylaxis
Ab-Mediated/Cytotoxic (Type II)	IgG or IgM antibodies deposit and bind to cell membrane- or matrix-associated antigen leading to lysis of the target cell	Autoimmune hemolytic anemia, anti-glomerular basement membrane disease (Goodpasture syndrome), Graves' disease, pemphigus vulgaris, rheumatic fever, ITP
Immune Complex (Type III)	Ag-Ab complexes deposit in tissues, which activates complement and recruits inflammatory mediators, resulting in tissue injury	SLE, PAN, post-streptococcal glomerulonephritis, serum sickness, viral hepatitis
Cell-Mediated/Delayed Hypersensitivity (Type IV)	Release of cytokines by sensitized T cells and T cell-mediated cytotoxicity	Contact dermatitis, insect venom, mycobacterial proteins (e.g. tuberculin skin test)

Immunogenetics and Disease

- the short arm of chromosome 6 contains the genes that encode HLA molecules
- in humans, HLAs act as MHCs which a) present antigens to be recognized by T-cell receptors and b) identify the self to the immune system, such that they must be matched for in organ transplantation
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases

Table 2. Classes of MHCs

MHC Class	Types	Location	Function
I	HLA-A, B, C	All nucleated cells	Recognized by CD8+ (cytotoxic) T lymphocytes
II	HLA-DP, DQ, DR	Ag presenting cells (mononuclear phagocytes, B cells, etc.)	Recognized by CD4+ (helper) T lymphocytes
III	Some components of the complement cascade	In plasma	Chemotaxis, opsonization, lysis of bacteria and cells

Table 3. HLA-Associated Rheumatic Diseases

HLA Type	Associated Conditions	Comments
B27	AS ReA EA (axial) PsA (axial)	Relative risk = 20x for developing AS and ReA
DR4, DR1	RA	In RA, relative risk = 2-10x; found in 93% of patients
DR3	SS SLE	DR3 is associated with the production of anti-Ro/SSA and anti-La/SSB antibodies

Differential Diagnoses of Common Presentations

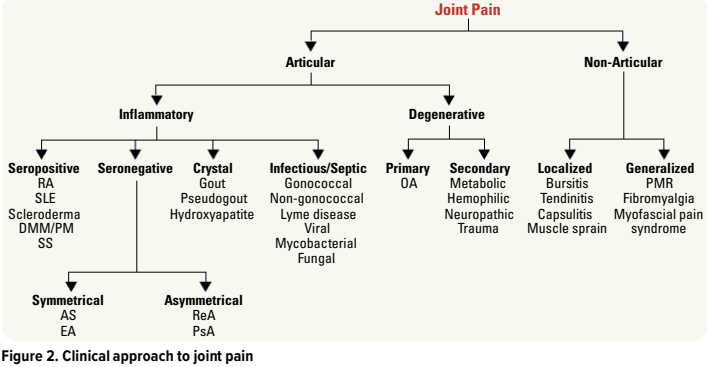

Figure 2. Clinical approach to joint pain

Table 4. Differential Diagnosis of Acute Monoarthritis

Non-Inflammatory	Inflammatory		
	Crystal-Induced	Infectious	Seronegative
Hemarthrosis, internal derangement (e.g. loose body, torn meniscus)	Monosodium urate (MSU-gout), CPPD/pseudogout, hydroxyapatite	Gonococcal, non-gonococcal, mycobacterial, and fungal	AS, PsA, ReA

Table 5. Differential Diagnosis of Oligoarthritis/Polyarthritis

Acute (<6 wk)	Chronic (>6 wk)			
Post-viral infection (parvovirus B19, HIV) Post-bacterial infection (GC and non-GC, rheumatic fever) Crystal-induced Other (sarcoidosis, Lyme disease) Very early rheumatoid arthritis (VERA)	**Seropositive inflammatory arthritis** RA SLE Scleroderma DMM/PM	**Seronegative inflammatory arthritis** AS EA PsA ReA	**Degenerative** OA	**Crystal** Polyarticular gout

Key Cytokine Targets of Biologic Drugs

TNF
Source of cytokine: T cells, macrophages/monocytes
Major functions: apoptotic cell death, cachexia, induces other cytokines, T cell stimulation, induces metalloproteinases and prostaglandins, increases expression of adhesion molecules; increases vascular permeability, leading to increased entry of IgG, complement, and cells into tissues

Interleukin-6 (IL-6)
Source of cytokine: many cells including monocytes and macrophages
Major functions: anemia of inflammation (hepcidin production), proliferation of B and T cells, acute phase reactant, induces natural protease inhibitor, promotes erosions, induces elevated CRP

Adaptive Immune Cells
B cell: produces antibodies after activation by specific antigen and B cell co-receptor, additional signals provided by CD4+ T helper cells
Cytotoxic T cell: CD8+ cell, directs cytotoxicity of target cells at sites of infection, kills via lytic granules and FasL-Fas interaction, recognizes specific antigen and MHC I
Helper T cell: subset of CD4+ cells, activates and helps other types of cells carry out immune defense (activates macrophages, helps B cells, releases cytokines)
Regulatory T cell: subset of CD4+ cells, suppresses activation of naïve autoreactive T cells

Causes of Joint Pain

SOFTER TISSUE
Sepsis
OA
Fracture
Tendon/muscle
Epiphyseal
Referred
Tumour
Ischemia
Seropositive arthritides
Seronegative arthritides
Urate (gout)/other crystal
Extra-articular rheumatism (PMR/fibromyalgia)

Patterns of Joint Involvement
- Symmetrical vs. asymmetrical
- Small vs. large
- Mono vs. oligo (2-4 joints) vs. polyarticular (≥5 joints)
- Axial vs. peripheral

Table 6. Symptoms of Inflammatory Arthritis vs. Degenerative Arthritis

Inflammatory	Degenerative
Pain at rest, relieved with activity	Pain with motion, relieved by rest
Morning stiffness >1 h	Morning stiffness <1 h
Cardinal signs of inflammation (warmth, swelling, erythema, tenderness, loss of function)	Joint instability, buckling, gelling (short duration of stiffness (<1/2 h) after immobility)
Malalignment/deformity (late finding)	Bony enlargement, malalignment/deformity (late finding)
Extra-articular manifestations	Evening/end of day pain
Nighttime awakening due to pain	

Table 7. Seropositive vs. Seronegative Rheumatic Diseases

	Seropositive	Seronegative
Demographics	F>M	M>F
Peripheral Arthritis	Symmetrical Small (PIP, MCP) and medium joints (wrist, knee, ankle, elbow) common DIP not involved	Usually asymmetrical Usually larger joints, lower extremities (exception: PsA) DIP in PsA Dactylitis ("sausage digit")
Pelvic/Axial Disease	No (except for C-spine)	Yes
Enthesitis	No	Yes
Extra-Articular	Nodules Vasculitis Sicca Raynaud's phenomenon Rashes, internal organ involvement (lung, cardiac) Entrapment neuropathies (i.e. carpal tunnel syndrome)	Iritis (anterior uveitis) Oral ulcers Gastrointestinal Dermatological (psoriasis, nail pitting, onycholysis, keratoderma blenorrhagicum, or balanitis) Genitourinary inflammation

Synovial Fluid Analysis

- synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage

Indications

- diagnostic: to clarify cause of inflammation; to analyze fluid for culture, crystal, and cell count to differentiateinflammatory, degenerative, septic, crystal, and hemarthrosis
- therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection in the absence of sepsis

Contraindications to Joint Aspiration or Injection

- absolute: open lesion or suspected infection of overlying skin or soft tissue
- relative: bleeding diathesis, thrombocytopenia, prosthetic joint

Synovial Fluid Analysis

- most important to assess the 3 Cs: cell count (WBC) and differential, culture and Gram stain, and crystal analysis
- other parameters to consider are listed in Table 8

Table 8. Synovial Fluid Analysis

Parameter	Normal	Non-Inflammatory	Inflammatory	Septic	Hemorrhagic
Colour	Pale yellow	Pale yellow	Pale yellow	Yellow to white	Red/brown
Clarity	Clear	Clear	Opaque	Opaque/purulent	Sanguinous
WBC/mm^3	<200	<2000	≥2000 (crystal-induced arthritis – often much higher than 2000)	>50,000	Variable
% PMN	<25%	<25%	≥50%	>75%	Variable
Culture/Gram Stain	–	–	–	Usually positive	–
Examples		Trauma OA Neuropathy Hypertrophic – arthropathy	Seropositive Seronegative Crystal arthropathies	*S. aureus* Gram negative GC → difficult to culture (may have low WBC)	Trauma Hemophilia

The presence of synovitis often indicates articular as opposed to non-articular joint pain; synovitis presents with: soft tissue swelling, effusion, warmth, and stress pain (passive movement of the joint through its range, plus a little bit further)

Monitoring CRP vs. ESR

- CRP is more sensitive for inflammation than ESR
- CRP responds more quickly to changes in the clinical situation than ESR
- False negative and false positive results are more common with ESR
- ESR is increased by renal disease, female sex, older age, pregnancy, and other chronic diseases such as DM, multiple myeloma, and congestive heart failure
- ESR can be useful at detecting low-grade bone and joint infections and monitoring disease activity in CTDs such as SLE, PMR, and GCA
- Do not order ESR for acute inflammation

Enthesitis: inflammation of tendon or ligament at site of attachment to bone (e.g. achilles enthesitis, plantar fasciitis)

Most Important Tests of Synovial Fluid

3 Cs
Culture and Gram stain
Cell count and differential
Crystal examination

Septic Arthritis

Definition
- invasion of the joint by an infectious agent
- septic arthritis is a medical emergency; it can lead to rapid joint destruction and has a 10-15% risk of mortality
- knee and hip are most commonly affected joints, with knee accounting for approximately 50% of cases
- poor prognostic factors: older age, immunocompromised, delay in treatment, previously damaged joint, and joint prosthesis

Clinical Presentation
- acute onset of: joint pain, swelling, erythema, immobility, and warmth

Pathophysiology
- most commonly caused by hematogenous spread of bacterial infection (Gram-positive cocci > Gram-negative bacilli)

Risk Factors
- very young or very old age (>80 yr), portal of entry (IV drug use, hemodialysis), recent STI, RA (related to prior joint damage and immunosuppressed state of host), type 2 DM

Investigations
- synovial fluid analysis: WBC count with differential, crystal analysis, Gram stain, and culture (see *Table 8, RH4*)
- blood work: CBC and C&S
- ± endocervical, urethral, rectal, and oropharyngeal swabs (if gonococcal septic arthritis is suspected)
- ± plain x-ray to establish joint baseline and to monitor treatment

Treatment
- consider empiric IV antibiotic therapy until septic arthritis is excluded or until cultures come back to narrow antibiotic choice
- source control and joint decompression
- see Infectious Diseases, ID13 and Orthopedic Surgery, *Septic Joint* OR11

Choosing Wisely Canada Recommendations
1. Do not order ANA as a screening test in patients without specific signs or symptoms of SLE or another CTD
2. Do not order an HLA-B27 unless spondyloarthritis is suspected based on specific signs or symptoms
3. Do not repeat DEXA scans more often than every 2 yr
4. Do not prescribe bisphosphonates for patients at low risk of fracture
5. Do not perform whole body bone scans (e.g. scintigraphy) for diagnostic screening for peripheral and axial arthritis in the adult population
6. Do not prescribe opioids for management of chronic rheumatic diseases before optimizing the use of non-opioid approaches in pain management
7. Do not delay or avoid palliative symptom management and advance care planning for a patient with life-limiting rheumatic diseases because they are pursuing disease-directed treatment

Septic arthritis is a medical emergency; it leads to rapid joint destruction and there is a 10-15% risk of mortality

Degenerative Arthritis: Osteoarthritis

- see Family Medicine, FM44

Definition
- progressive deterioration of articular cartilage and surrounding joint structures caused by genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation

Classification (Based on Etiology)
- primary (idiopathic)
  - most common, unknown etiology
- secondary
  - post-traumatic or mechanical
  - post-inflammatory (e.g. RA) or post-infectious
  - heritable skeletal disorders (e.g. scoliosis)
  - endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
  - metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
  - neuropathic (e.g. Charcot joints), atypical joint trauma due to peripheral neuropathy (e.g. DM, syphilis)
  - AVN
  - other (e.g. congenital malformation)

Pathophysiology
- the process appears to be initiated by abnormalities in biomechanical forces and/or, less often, in cartilage
- elevated production of local pro-inflammatory cytokines is important in OA progression
- tissue catabolism > repair
- contributing factors (mechanisms unknown): genetics, alignment (bow-legged – varus, knock-kneed – valgus), joint deformity (hip dysplasia), joint injury (meniscal or ligament tears), obesity, environmental, mechanical loading, age, and gender
- considered to be a systemic musculoskeletal disorder rather than a focal disorder of synovial joints

Epidemiology
- most common arthropathy (accounts for ~75% of all arthritides)
- increased prevalence with increasing age (35% of 30 y/o, 85% of 80 y/o)

Risk Factors
- genetic predisposition, advanced age, obesity (for knee and hand OA), female, and trauma

OA of MCPs can be seen in hemochromatosis or CPPD-related disease (chondrocalcinosis)

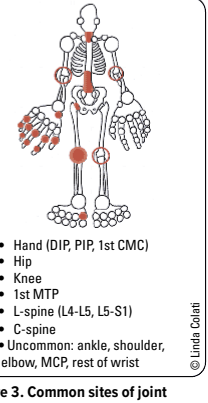

Figure 3. Common sites of joint involvement in OA

Table 9. Signs and Symptoms of OA

Signs	Symptoms
Joint line tenderness; stress pain ± joint effusion	Joint pain with motion; relieved with rest
Bony enlargement at affected joints	Gelling
Malalignment/deformity (angulation)	Joint instability/buckling (often due to ligamentous instability)
Limited ROM	Joint locking due to "joint mouse" (bone or cartilage fragment)
Crepitus on passive ROM	Loss of function (e.g. meniscal tear or other internal derangements)
Inflammation (mild if present)	Insidious onset of pain, localized to affected joints
Periarticular muscle atrophy	Fatigue, poor sleep, impact on mood

Table 10. Radiographic Hallmarks of OA

Radiographic Hallmarks of Osteoarthritis	Radiographic Hallmarks of Inflammatory Arthritis
Joint space narrowing – typically non-uniform	Joint space narrowing – typically uniform
Subchondrial sclerosis	Soft tissue swelling
Subchondrial cyst formation	Erosions
Osteophytes	Periarticular osteopenia
Knee, hip, DIP joints	Rheumatoid: C-spine, carpus, MCP joints, MTP joints
Older, overused joint	Often younger
	New bone formation (i.e. psoriatic arthritis)

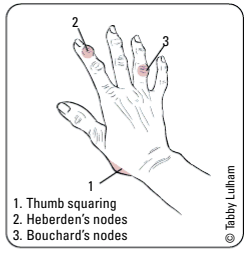

Figure 4. Hand findings in OA

Joint Involvement

- generalized OA: 3+ joint groups
- asymmetric (knees usually affected bilaterally)
- hand
  - DIP (Heberden's nodes = osteophytes → enlargement of joints)
  - PIP (Bouchard's nodes)
  - CMC (usually thumb squaring)
  - 1st MCP (other MCPs are usually spared)
- hip
  - usually presents as groin pain ± dull or sharp pain in the trochanteric area, internal rotation and abduction are lost first
  - pain can radiate to the anterior thigh but generally does not go below the knee
- knee
  - initial narrowing of one compartment, medial > lateral; seen on standing x-rays, often patellofemoral joint involved
- foot
  - common in 1st MTP and midfoot
- lumbar spine
  - very common, especially L4-L5, L5-S1
  - degeneration of intervertebral discs and facet joints
  - reactive bone growth can contribute to neurological impingement (e.g. sciatica, neurogenic claudication) or spondylolisthesis (forward or backward movement of one vertebra over another)
- cervical spine
  - commonly presents with neck pain that radiates to scapula, especially in mid-lower cervical area (C5-C6)

Investigations

- blood work
  - normal CBC, ESR, and CRP
  - negative RF and ANA
- radiology: 4 hallmark findings, see sidebar
- synovial fluid: non-inflammatory (see *Table 8, RH5*)

Treatment

- presently, no treatment alters the natural history of OA
- prevention: prevent injury, weight management, physical activity (maintenance of muscle strength)
- non-pharmacological therapy
  - weight loss (minimum 5-10 lb loss) if overweight
  - exercise: more effective if supervised, often by physiotherapists or in a class setting; Tai chi is strongly recommended for hip/knee OA
  - self-efficacy and self-management programs (goal-setting, positive thinking, education on the disease)
  - thermal intervention: heat or cold
  - occupational therapy: aids, splints, cane, walker, bracing
- pharmacological therapy (see *Table 35, RH31*)
  - stepped approach to therapy (local → systemic therapy)
  - local therapy:
    - topical NSAIDs, topical capsaicin (knee, hand OA)
    - injections: IA glucocorticoids (knee, hip OA)
  - systemic therapy:
    - acetaminophen, oral NSAIDs
    - centrally acting agents (e.g. duloxetine)
  - the following are not recommended based on lack of high-quality evidence: opioids and medical cannabinoids (for pain), hyaluronates, platelet-rich plasma, stem cell injections, chondroitin, and glucosamine
- surgical treatment
  - total and/or partial joint replacement, joint debridement (not shown to be effective), osteotomy, fusion

Differential Diagnosis of Elevated ESR

Systemic inflammatory diseases
Localized inflammatory diseases
Malignancy
Trauma
Infection
Tissue injury/ischemia

The Radiographic Hallmarks of OA

LOSS
Loss of joint space
Osteophytes
Subchondral cysts
Subchondral sclerosis

Exercise for Osteoarthritis of the Knee:
A Cochrane Systematic Review
Br J Sports Med 2015;49:1554-1557
Purpose: To determine if land-based therapeutic exercise is beneficial for people with knee OA in reducing pain, improving physical function, and improving quality of life.
Methods: Five databases searched for randomized clinical trials comparing therapeutic exercise with a non-exercise control.
Results: 54 studies identified. Results from 44 trials indicate that exercise significantly reduced pain (12 points/100; 95% CI 10 to 15) and improved physical function (10 points/100; 95% CI 8 to 13) after treatment. Additionally, 13 studies showed improved quality of life with exercise. 12 studies showed reduced knee pain (6 points/100; 95% CI 3 to 19) and 10 studies showed improved physical function (3 points/100; 95% CI 1 to 5) with exercise 2-6 mo after treatment.
Conclusion: In people with knee OA, land-based therapeutic exercise provides short-term benefit that is sustained a few mo after treatment.

Seropositive Rheumatic Disease

- diagnosis vs. classification in rheumatology
  - diagnostic criteria are selected for sensitivity as opposed to specificity and thus may misdiagnose some cases
  - classification criteria are developed for specificity so well-defined cases can be studied in clinical trials
  - modern classification criteria are more sensitive and specific for diagnostic use in studies of earlier disease
- seropositive arthropathies are characterized by the presence of a serologic marker such as positive RF or ANA
- a small subset of the vasculitides (i.e. the small vessel ANCA-associated vasculitides) has a measurable serological component, but they are often considered a separate entity from seropositive disease by experts

Table 11. Autoantibodies and Their Prevalence in Rheumatic Diseases

Autoantibody	Disease	Healthy Controls	Comments
RF	RA 80% SS 50% SLE 20%	5-25%	Serologic hallmark of RA Autoantibodies directed against Fc domain of IgG Sensitive in RA (can be negative early in disease course) +RF is associated with more aggressive joint disease and extra-articular features (e.g. nodules) May be present in ANA-positive diseases, often in lower titre Nonspecific; may be present in IE, TB, hepatitis C, silicosis, sarcoidosis
Anti-CCP	RA 80%		Specific for RA (94-98%) May be useful in early disease and to predict persistent and erosive disease; can occur before clinical disease becomes apparent Associated with increased extra-articular RA manifestations
ANA	SLE 98% MCTD 100% SS 40-70% CREST syndrome 60-80% (Often seen in other CTDs)	High titres 1:640 <5% Low titres 1:40 Up to 30%, Prevalence of non-disease-related ANA rises with age	Ab against nuclear components (DNA, RNA, histones, centromere) Sensitive but not specific for SLE Given high false positive rate - only measure when high pre-test probability of CTD Given its high sensitivity, a negative ANA can help to rule out SLE
Anti-dsDNA	SLE 50-70%	0%	Specific for SLE (95%) Levels can correlate with disease activity (i.e. SLE flare)
Anti-Sm	SLE <30%	0%	Specific but not sensitive for SLE Does not correlate with SLE disease activity If positive, will remain positive through disease course
Anti-Ro (SSA)	SS 40-95% SSc 21% SLE 32% RA 15%	0.5%	Seen in SS Also seen in subacute cutaneous SLE (74%) May be the only Ab present in ANA-negative SLE Presence in pregnancy increases risk of having a child with neonatal lupus syndrome and congenital heart block
Anti-La (SSB)	SS 40% SLE 10%	0%	Usually occurs with anti-Ro Specific for SS and SLE when anti-Ro is also positive Increases risk of having a child with neonatal lupus syndrome
Antiphospholipid (LAC, aCLA, aB2GP)	APS 100% SLE 31-40%	<5%	By definition, present in APS Only small subset of SLE patients develop clinical syndrome of APS If positive, will often get a false positive VDRL test
Anti-Histone	Drug-induced SLE 95% SLE 30-80%	0% 0%	Highly specific for drug-induced SLE
Anti-RNP	MCTD 20% SLE		High titres present in MCTD; present in many other CTDs (especially SLE)
Anti-Centromere	Limited SSc (CREST) >80%	0%	Specific for CREST, limited cutaneous variant of systemic sclerosis
Anti-Topoisomerase I (formerly Scl-70)	Diffuse SSc 26-76%	0%	Specific for SSc Increased risk for pulmonary fibrosis in SSc
Anti-Jo1	PM DMM	0%	Less frequent for DMM Associated with interstitial pulmonary fibrosis and anti-synthetase syndrome
c-ANCA	Active GPA 90% MPA 25% EGPA <5%	0%	Specific 80-95% for GPA Sensitivity can vary between moderate to high depending on technique and timing of sample. Enzyme-linked immunosorbent assay (ELISA) method (anti-PR3) is more specific than immunofluorescent technique (IF)
p-ANCA	GPA 10% MPA 50-60% EGPA 50-70%	0%	Nonspecific and poor sensitivity (found in ulcerative colitis, PAN, microscopic polyangiitis, EGPA, rapidly progressive glomerulonephritis). ELISA method (anti-MPO) is more specific than IF
Anti-Mi-2	DMM 15-20%		Specific but not sensitive (not available in all centres)
Ab Against RBCs, WBCs, or Platelets	SLE		Perform DAT, test Hb, reticulocyte, leukocyte, platelet count, and antiplatelet Abs
Anti-Mitochondria	Primary biliary cholangitis	0%	Sensitive and specific

Note: some individuals in the normal population test positive for RF and/or ANA, but do not have the conditions listed above

Connective Tissue Disorders

Table 12. Features of Seropositive Arthropathies

	RA	SLE	Scleroderma	DMM
CLINICAL FEATURES				
History	Symmetrical polyarthritis (small joint involvement) Morning stiffness (>1 h) Dyspnea on exertion (ILD) in <30%	Multisystem disease: rash, mouth ulcers, photosensitivity, Raynaud's, alopecia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis	Skin tightness, stiffness of fingers, Raynaud's, heartburn, dysphagia, SOB on exertion due to pulmonary HTN or ILD, renal crisis with new onset HTN or hypertensive urgency/emergency	Heliotrope rash (periorbital), Gottron's papules (violaceous papules over knuckles and IPs) ± poikiloderma Shawl sign: photosensitivity, macular erythema over chest and shoulder Proximal muscle weakness > pain, dyspnea on exertion
Physical Examination	Early: effused joints, tenosynovitis, subcutaneous nodules, other extra-articular manifestations Late: joint deformities, bone-on-bone crepitus in advanced disease, inspiratory crackles	Check BP, rash, mouth ulcers, alopecia, Raynaud's phenomenon, serositis, ± effused (typically small) joints (can be minimal, look for soft tissue swelling)	Skin tightness on dorsum of hand, facial skin tightening, telangiectasia, calcinosis, non-effused joints, inspiratory crackles, features of right-sided heart failure	Heliotrope rash, Gottron's papules, shawl sign, proximal muscle weakness (usually painless), inspiratory crackles
LABORATORY				
Nonspecific	↑ ESR in 50-60% ↑ CRP ↑ Platelets ↓ Hb (chronic disease) ↓ WBC (neutropenia rare)	↑ ESR ↓ Platelets (autoimmune) ↓ Hb (autoimmune) ↓ WBC (leukopenia, lymphopenia) ↑ Cr, proteinuria, RBC casts	↓ Hb Normal WBC Possibly ↑ Cr, proteinuria	↑ CRP ↓ Hb Normal WBC ↑CK
Specific	RF-positive in ~80% Anti-CCP-positive in ~80%	ANA-positive in 98%, Anti-dsDNA-positive in 50-70%, Anti-Sm-positive in 30%, ↓ C3, C4, total hemolytic complement, false positive VDRL (in SLE subtypes) APLA	ANA-positive in >90% Anti-topoisomerase 1 (diffuse) Anti-centromere (usually in CREST, see Sidebar, *CREST Syndrome, RH14*)	CK elevated in 80% ANA-positive in 33% Anti-Jo-1, anti-Mi-2 Muscle biopsy EMG MRI
Radiographs	Very early: normal Early: periarticular osteopenia Later: joint space narrowing Erosions Symmetric/concentric + ILD/lung nodules	Non-erosive ± Osteopenia ± Soft tissue swelling	± ILD ± Esophageal dysmotility ± Calcinosis	± Esophageal dysmotility ± ILD ± Calcifications

Rheumatoid Arthritis

Definition

- chronic, symmetric, erosive synovitis of peripheral joints (e.g. wrists, MCPs, MTPs)
- characterized by inflammatory joint disease ± a number of extra-articular features
- 1 joint with definite clinical synovitis (swelling) not explained by another disease

Table 13. 2010 ACR/EULAR Classification Criteria for RA

(score-based algorithm: add score of categories A-D; a score of 6/10 for definite RA)

Criteria	Score	Comments
A. Joint involvement (swollen or tender)		
1 large joint (shoulders, elbows, hips, knees, and ankles)	0	
2-10 large joints	1	
1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs)	2	
4-10 small joints	3	
>10 joints (at least 1 small joint)	5	
B. Serology		Total score of ≥6: definite RA Must have ≥1 joint with definite clinical swelling, not better explained by another disease
Negative RF and negative Anti-CCP	0	
Low-positive RF or low-positive Anti-CCP (<3x ULN)	2	
High-positive RF or high-positive Anti-CCP (>3x ULN)	3	
C. Acute phase reactants		
Normal CRP and normal ESR	0	
Abnormal CRP and abnormal ESR	1	
D. Duration of symptoms		
<6 wk	0	
≥6 wk	1	

Arthritis Rheum 2010;62:2569-2581

RA is an independent risk factor for atherosclerosis and CV disease. RA is associated with increased overall mortality/morbidity from all causes: CV disease, neoplasm (especially lymphoma), infection

Common Presentation

- Morning stiffness >1 h, improves with use
- Symmetric joint involvement
- Initially involves small joints of hands and feet
- Constitutional symptoms

Pathophysiology

- autoimmune disorder, unknown etiology; may have genetic and environmental component
- complex genetic and environment interactions lead to disruption of immune tolerance, ultimately resulting in synovial inflammation
  - genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type), cytokine promoters, T cell signaling
  - environmental predisposition: induction of enzymes that convert arginine to citrulline caused by environmental stress (cigarette smoking), propensity for immune reactivity to neoepitopes created by protein citrullination
- inflammatory process causes transformation of synovium into an invasive pannus tissue that degrades cartilage and bone with absence of repair
  - elevated TNF level increases osteoclasts and decreases osteoblasts at the site of inflammation (results in periarticular osteopenia)
  - upregulation of RANK ligand increases osteoclast-mediated destruction

Epidemiology

- most common inflammatory arthritis: prevalent in 1% of population
- F:M=3:1
- age of onset commonly between 20-40 yr

Clinical Presentation

- variable course of exacerbations and remissions
- morning stiffness >1 h, improves with use, worsens with rest
- polyarthritis: symmetric joint involvement (tender, swollen), small joints affected, most commonly in hands and feet (MCP, PIP, MTP)
- constitutional symptoms: profound fatigue, depression, myalgia, weight loss
- extra-articular features
- functional limitation and decrease in global functional status
- complications of chronic synovitis
  - signs of mechanical joint damage: loss of motion, instability, deformity, crepitus, joint deformities
    - swan neck deformity, boutonnière deformity
    - ulnar deviation and subluxation of MCP, radial deviation of wrist joint
    - hammer toe, mallet toe, claw toe
    - flexion contractures
  - atlanto-axial and subaxial subluxation
    - C-spine instability
      - neurological impingement (long tract signs)
      - difficult/dangerous intubation: risk of worsening subluxation and damage to spinal cord
- limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
- tenosynovitis → may cause rupture of tendons
- carpal tunnel syndrome
- ruptured Baker's cyst (outpouching of synovium behind the knee); presentation similar to acute deep vein thrombosis (DVT)
- poor prognostic factors include: young age of onset, high RF titre, elevated ESR, activity of >20 joints, and presence of extra-articular features

Table 14. Extra-Articular Features of RA Classified by Underlying Pathophysiology

System	Vasculitic	Lymphocytic Infiltrate
Skin	Periungual infarction, cutaneous ulcers, palpable purpura	Rheumatoid nodules (may have vasculitic component)
Ocular	Episcleritis, scleritis	Keratoconjunctivitis sicca
Head and Neck		Xerostomia, Hashimoto's thyroiditis (see Endocrinology, E31)
Cardiac		Peri-/myocarditis, valvular disease, conduction defects
Pulmonary		Pulmonary fibrosis, pleural effusion, pleuritis, pulmonary nodules
Neurologic	Peripheral neuropathy: sensory stocking-glove, mononeuritis multiplex	
Hematologic		Splenomegaly, neutropenia (Felty's syndrome)
Renal		Amyloidosis – caused by accumulation of abnormal proteins

Classification of Global Functional Status in RA

- Class I: able to perform usual activities of daily living (self-care, vocational, avocational)
- Class II: able to perform self-care and vocational activities, restriction of avocational activities
- Class III: able to perform self-care, restriction of vocational and avocational activities
- Class IV: limited ability to perform self-care, vocational, and avocational activities

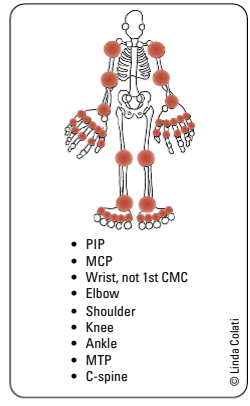

Figure 5. Common sites of joint involvement in RA

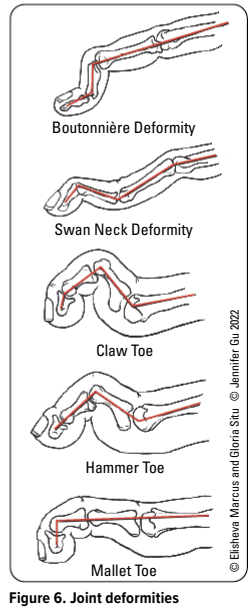

Figure 6. Joint deformities

Syndromes in RA
SS (common): keratoconjunctivitis sicca and xerostomia (dry eyes and mouth)
Caplan's syndrome (very rare): combination of RA + pneumoconiosis that manifests as multiple intrapulmonary nodules
Felty's syndrome (rare): arthritis, splenomegaly, neutropenia

Investigations

- blood work
  - RF: 80% sensitivity but non-specific; may not be present at onset of symptoms; levels do not correlate with disease activity
    - can be associated with more erosions, more extra-articular manifestations, and worse function
  - anti-CCP: 80% sensitivity but more specific (94-98%); may precede onset of symptoms
- increased disease activity is associated with decreased Hb (anemia of chronic disease) and increased platelets, ESR, and CRP
- imaging
  - bilateral hands/wrists, ankles/feet x-ray
    - first change is periarticular osteopenia, followed by erosions
  - C-spine x-ray (may be normal at onset, required for preoperative assessment in long-standing disease)
  - U/S (with power Doppler) – often changes of synovitis/erosion noted in advance of those seen on plain x-ray
  - MRI may be used to image hands to detect early synovitis and erosions
  - on MRI, inflamed synovium is hypointense on T1 and hyperintense on T2; bone marrow edema can be seen as well as areas of increased uptake gadolinium contrast

Treatment

- goals of therapy: remission or lowest possible disease activity
  - key is early diagnosis and early intervention with DMARDs
  - "window of opportunity" = early treatment within first 3 mo of disease may allow for better control/remission
  - assess poor prognostic factors at baseline (RF-positive, functional limitations, and extra-articular features)
- behavioural
  - exercise program: active, gentle ROM and isometric exercise during flares; aquatic/aerobic/strengthening exercise between flares
  - job modification, assistive devices as necessary
  - interventions to reduce cardiovascular disease, smoking cessation, lipid control
- pharmacologic: alter disease progression
  - DMARDs and biologics (not analgesics or NSAIDs) can alter the course of RA
  - DMARDs
    - treatment with DMARDs should be started as soon as RA diagnosis is made and should be aimed at reaching sustained remission
    - MTX is the gold standard and is first-line unless contraindicated
      - prior to MTX therapy: CBC profile, liver enzymes (ALT), Cr (Cr clearance), hepatitis B and C serology, and a CXR should be done
      - monitor and if inadequate response (3-6 mo) → combine or switch
      - consider combination therapy with MTX if patients have poor prognostic features or high disease activity
      - therapy includes: hydroxychloroquine, SSZ, leflunomide, biologics
      - contraindications include liver disease, significant alcohol intake, pregnancy, and lactation
      - if contraindication to MTX, then hydroxychloroquine, SSZ, and/or leflunomide should be considered with the former being considered as a weaker agent and the latter as more potent
    - JAK inhibitors (including tofacitinib and upadacitinib) are oral small molecule synthetic DMARDs; considered if other DMARDs fail
  - biologics (bDMARDs)
    - should be used if inadequate response to DMARDs
    - should be combined with DMARD therapy (initiating with combination therapy is associated with faster response rates and longer duration of effect)
    - first-line (anti-TNF) options: infliximab, etanercept, adalimumab, golimumab, and certolizumab
    - non-anti-TNF biologic agents include anakinra (almost never used for RA), abatacept, rituximab, and tocilizumab
    - reassess every 3-6 mo and monitor disease activity (predominantly via assessing swollen joint count)
- pharmacologic: supportive to reduce inflammation and pain
  - NSAIDs
    - individualize according to efficacy, tolerability, and comorbidities
    - contraindicated/cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy, CKD, anticoagulant use)
    - add acetaminophen for synergistic pain control
  - corticosteroids
    - local: injections to control symptoms in a specific joint

Poor prognostic features of RA include: young age of onset, high RF titre, elevated ESR, activity of >20 joints, and presence of extra-articular features

Side Effects of Steroids

- Weight gain
- Osteoporosis
- AVN
- Cataracts, glaucoma
- PUD
- Susceptibility to infection
- Easy bruising
- Acne
- HTN
- Hyperlipidemia
- Hypokalemia, hyperglycemia
- Mood swings

DMARDs, prednisone, and biologics (bDMARDs) but not analgesics or NSAIDs, alter the course of RA

- systemic (oral prednisone) or IM
  - low dose (5-10 mg/d) useful for short-term to improve symptoms if NSAIDs are ineffective and to bridge gap until DMARDs take effect
  - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy (e.g. bisphosphonates) if using corticosteroids 7.5 mg/d >3 mo, particularly in those with other risk factors
  - cautions/contraindications: active infection, TB, osteoporosis, HTN, gastric ulcer, DM
- surgical
  - indicated for structural joint damage
  - surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair

Follow-Up Management and Clinical Outcomes

- clinical reassessment every mo initially, then 3-6 mo if still ongoing activity, then 6-12 mo after inflammation has been suppressed
- examine joints for active inflammation – if active, consider adjusting medications, physical therapy/occupational therapy (PT/OT)
- RA patients should be screened and managed for cardiovascular disease given increased risk
- if assessment reveals joint damage – consider analgesia, referral to PT/OT, surgical options
- outcome depends on disease activity, joint damage, physical functional status, psychological health, and comorbidities
- functional capacity is a useful tool for determining therapeutic effectiveness; many tools for evaluation have been validated
- patients with RA have an increased prevalence of other serious illnesses: infection (e.g. pulmonary, skin, joint), osteoporosis, mental health disorders, renal impairment, lymphoproliferative disorders, cardiovascular disease (correlates with disease activity and duration)
- risk of premature mortality, decreased life expectancy (most mortality not directly caused by RA)

Systemic Lupus Erythematosus

- see Nephrology, NP26

Definition

- chronic autoimmune disease of unknown etiology resulting in multi-system inflammation
- characterized by production of autoantibodies and diverse clinical manifestations

Table 15. Classification Criteria of SLE*

Entry criterion: ANA at a titre of ≥1:80 and Additive Criteria 1. Do not count criterion if there is a more likely explanation than SLE 2. Occurrence of a criterion on at least one occasion is sufficient 3. Within each domain, only the highest weighted criterion is counted towards the total score		
Clinical Domains and Criteria		**Score**
Constitutional	Fever	2
Hematologic	Leukopenia	3
	Thrombocytopenia	4
	Autoimmune hemolysis	4
Neuropsychiatric	Delirium	2
	Psychosis	3
	Seizure	5
Mucocutaneous	Non-scarring alopecia	2
	Oral ulcers	2
	Subacute cutaneous or discoid lupus	4
	Acute cutaneous lupus	6
Serosal	Pleural or pericardial effusion	5
	Acute pericarditis	6
Musculoskeletal	Joint involvement	6
Renal	Proteinuria (>0.5 g/24 h)	4
	Renal biopsy Class II or V lupus nephritis	8
	Renal biopsy Class III or IV lupus nephritis	10
Immunology Domains and Criteria		**Score**
Antiphospholipid antibodies	Anti-cardiolipin antibodies or Anti-β2PG1 antibodies or lupus anticoagulant	2
Complement proteins	Low C3 or low C4	3
	Low C3 and low C4	4
SLE specific antibodies	Anti-dsDNA or Anti-Sm antibodies	6

*Classification of SLE requires total score of ≥10 with ≥1 clinical criterion

Sindhu R. Johnson, Thomas Dörner, Ray Naden, et al. Arthritis & Rheumatology (71, 9), p. 1400, copyright © 2020, Modified by Permission of John Wiley and Sons

Diagnostic Criteria of SLE

MD SOAP BRAIN
Malar rash
Discoid rash
Serositis
Oral ulcers
ANA
Photosensitivity
Blood
Renal
Arthritis
Immune
Neurologic

A Systematic Review of Guidelines for Managing Rheumatoid Arthritis
BMC Rheumatol 2019;3:42
Five general principles for management:
- Start DMARDs as soon as possible following the diagnosis.
- The best initial treatment is MTX.
- Monitor disease activity regularly.
- Biologics should be initiated in patients with persistently active disease despite MTX treatment.
- Goals of treatment should be aimed at low disease activity or remission.

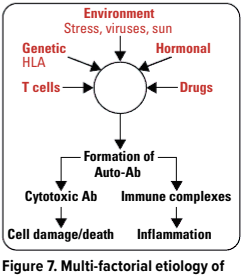

Figure 7. Multi-factorial etiology of SLE

Etiology and Pathophysiology

- production of cytotoxic autoantibodies and immune complex formation
- multi-factorial etiology
- **genetics**
  - common association with HLA-B8/DR3; ~10% have positive family history
  - strong association with defects in apoptotic clearance → fragments of nuclear particles captured by antigen-presenting cells → develop ANAs
  - cytokines involved in inflammatory process and tissue injury: BlyS, IL-6, IL-17, IL-18, TNF-α
- **environment**
  - UV radiation, cigarette smoking, infection, vitamin D deficiency, silica dust
- **estrogen**
  - increased incidence after puberty, decreased incidence after menopause
  - men with SLE have higher concentration of estrogenic metabolites
  - increased risk of SLE associated with use of combined oral contraceptive pills and hormone replacement therapy
- **infection**
  - viral (non-specific stimulant of immune response)
- **drug-induced**
  - antihypertensives (hydralazine), anticonvulsants (phenytoin), antiarrhythmics (procainamide), isoniazid, biologics
  - anti-histone Abs are commonly seen in drug-induced SLE
  - symptoms resolve with discontinuation of offending drug

Drug-Induced SLE
Often presents atypically with systemic features and serositis; usually associated with anti-histone Ab

Epidemiology

- prevalence: 0.05% overall
- F:M=10:1
- age of onset in reproductive yr (15-45)
- more common and severe in Hispanic and Asian individuals, and individuals of African descent
- bimodal mortality pattern
  - early (within 2 yr)
    - active SLE, active nephritis, infection secondary to steroid use
  - late
    - inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation

Clinical Presentation

- characterized by periods of flares and remission

Table 16. Signs and Symptoms of SLE

System	Symptoms
Systemic	Fatigue, malaise, weight loss, fever, lymphadenopathy
Hematologic	Anemia of chronic disease, hemolytic anemia, leukopenia, neutropenia, thrombocytopenia, pancytopenia, thrombosis, splenomegaly
Renal	Hematuria, proteinuria (glomerulonephritis), HTN, peripheral edema, renal failure
Dermatologic	Photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura, panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria
Musculoskeletal	Polyarthralgias, polyarthritis, myalgias, AVN, reducible deformities of hand (Jaccoud's arthritis)
Ophthalmic	Keratoconjunctivitis sicca, episcleritis, scleritis, cytoid bodies (cotton wool exudates on fundoscopy = infarction of nerve cell layer of retina)
Cardiac	Pericarditis, CAD, non-bacterial endocarditis (Libman-Sacks), myocarditis
Vascular	Raynaud's phenomenon, livedo reticularis (mottled discolouration of skin due to narrowing of blood vessels, characteristic lacy or net-like appearance), vasculitis Note: SLE is an independent risk factor for atherosclerosis and CAD
Respiratory	Pleuritis, ILD, pulmonary HTN, PE, alveolar hemorrhage
Gastrointestinal	Pancreatitis, SLE enteropathy, hepatitis, hepatomegaly, dysphagia, esophagitis, intestinal pseudo-obstruction, peritonitis, mesenteric vasculitis
Neurologic/Psychiatric	Seizures, stroke, delirium, psychosis
Life/Organ-Threatening	Cardiac: coronary vasculitis, malignant HTN, tamponade Hematologic: hemolytic anemia, neutropenia, thrombocytopenia, TTP, thrombosis Neurologic: seizures, CVA, stroke Respiratory: pulmonary HTN, pulmonary hemorrhage, emboli

Raynaud's Phenomenon
Vasospastic disorder characteristically causing discolouration of fingers and toes (white → blue → red)
Classic triggers: cold and emotional stress

Investigations

- ANA (98% sensitivity, but poor specificity → used as a screening test; ANA titres are not useful to follow disease course, see *Choosing Wisely Recommendations, RH5*)
- anti-dsDNA and anti-Sm are specific (95-99%)
- anti-dsDNA titre and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant (anti-dsDNA increases, C3 and C4 decrease with disease activity)
- APLA (anti-cardiolipin Ab, lupus anticoagulant, anti-β2 glycoprotein-I Ab), may cause increased risk of clotting and increased aPTT

Consider SLE in a patient who has involvement of 2 or more organ systems

Treatment

- **goals of therapy**
  - aim for remission, prevention of flares
  - hydroxychloroquine ± glucocorticoid
  - treat early and avoid long-term steroid use, if unavoidable see Endocrinology, E47 for osteoporosis management
  - if high doses of steroids are necessary for long-term control, taper when possible and add immunosuppressive therapies (MTX, azathioprine, mycophenolate)
  - treatment is tailored to organ system involved and severity of disease
  - moderate refractory disease can be treated with belimumab
  - all medications used to treat SLE require periodic monitoring for potential toxicity
- **dermatologic**
  - sunscreen, avoid UV light and estrogens
  - topical steroids, hydroxychloroquine
- **musculoskeletal**
  - NSAIDs ± gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
  - hydroxychloroquine improves long-term control and prevents flares
  - bisphosphonates, calcium, vitamin D to combat osteoporosis
- **other considerations**
  - smoking cessation
  - immunizations (influenza); live vaccines are generally not recommended
  - for women with APLA, avoid estrogen-containing contraceptives because of increased risk of thrombosis
- **organ-threatening disease**
  - high-dose oral prednisone or IV methylprednisolone in severe disease
  - steroid-sparing agents: azathioprine, MTX, mycophenolate (can use mofetil or sodium)
  - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or lupus nephritis)
  - low-dose IV cyclophosphamide or mycophenolate mofetil can be used for induction treatment in active lupus nephritis
  - refractory disease can be treated with rituximab or anifrolumab (a monoclonal antibody that blocks the action of a group of proteins called Type I Interferons)

The arthritis of SLE can be deforming but it is non-erosive (in contrast to RA) – called Jaccoud's arthritis

Antiphospholipid Antibody Syndrome

Definition

- multi-system vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions, and thrombocytopenia
- circulating antiphospholipid autoantibodies interfere with coagulation
- primary APS: occurs in the absence of other disease
- secondary APS: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- catastrophic APS: development within 1 wk of small vessel thrombotic occlusion in ≥3 organ systems with positive APLA (high mortality)

Manifestations of APLA
Thromboembolic events
Spontaneous abortions
Thrombocytopenia
Associated with livedo reticularis, migraine headaches

Arterial and venous thrombosis are usually mutually exclusive

Table 17. Classification Criteria of APS*

Criteria	Description
CLINICAL	
Vascular thrombosis	One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ Must be confirmed by imaging or histopathology
Pregnancy morbidity	≥1 death of morphologically normal fetus (confirmed by U/S or fetal exam) at ≥10 wk gestation; OR ≥1 premature birth of morphologically normal neonate before 34 wk gestation due to eclampsia, preeclampsia, or placental insufficiency; OR ≥3 consecutive spontaneous abortions <10 wk gestation (excluding maternal anatomic and hormonal abnormalities or paternal/maternal chromosomal causes)
LABORATORY	Labs must be positive on 2 occasions, at least 12 wk apart
Lupus anticoagulant	Present in plasma, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
Anti-cardiolipin Ab	IgG and/or IgM, plasma or serum, present in medium-high titre (i.e. >40 GPL or MPL, or >99th percentile), measured by ELISA
Anti-β2 glycoprotein-I Ab	IgG and/or IgM, plasma or serum, present in high titre (i.e. >99th percentile), measured by ELISA

* 1 clinical and 1 laboratory criteria must be present
J Thromb Haemost 2006;4:295-306

See *Landmark Rheumatology Trials, RH32* for more information on the TULIP-2 trial. It examined the efficacy of anifrolumab for the treatment of SLE.

Clinical Presentation

- see clinical criteria (*Table 17*)
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud's phenomenon, purpura, leg ulcers, gangrene

Treatment
- thrombosis
  - lifelong anticoagulation with warfarin
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent event, target INR 2-3 or 3-4 (recurrent events) for arterial event, or target INR 2.0-3.0 + ASA may be considered
- obstetric APS
  - heparin/low molecular weight heparin ± ASA during pregnancy
  - continuation of heparin at prophylactic dose for 6 wk after delivery should be considered to reduce the risk of maternal thrombosis
- catastrophic APS
  - high-dose steroids, anticoagulation, cyclophosphamide, plasmapheresis
  - any triggering factor (e.g. infections, malignancy) should be treated accordingly
  - refractory cases: B cell depletion (e.g. rituximab) or complement inhibition (e.g. eculizumab) may be considered

Scleroderma (i.e. Systemic Sclerosis)

Definition
- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction causing fibrosis

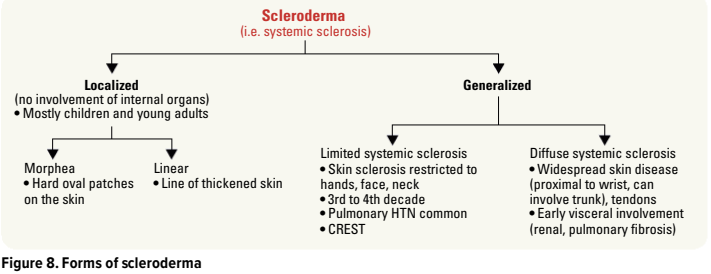
Scleroderma
(i.e. systemic sclerosis)
Localized
(no involvement of internal organs)
• Mostly children and young adults
Generalized
Morphea
• Hard oval patches on the skin
Linear
• Line of thickened skin
Limited systemic sclerosis
• Skin sclerosis restricted to hands, face, neck
• 3rd to 4th decade
• Pulmonary HTN common
• CREST
Diffuse systemic sclerosis
• Widespread skin disease (proximal to wrist, can involve trunk), tendons
• Early visceral involvement (renal, pulmonary fibrosis)

Figure 8. Forms of scleroderma

Etiology and Pathophysiology
- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
  - characterized by several hallmark pathogenic features: small vessel vasculopathy resulting in tissue hypoxia, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix
  - resembles malignant HTN
  - lung disease is the most common cause of morbidity and mortality

Table 18. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Criteria for the Classification of Scleroderma*

Item	Sub-item	Score
1. Skin thickening of fingers of both hands extending proximal to the MCP (sufficient criterion)		9
2. Skin thickening of the fingers	Puffy fingers Sclerodactyly	2
3. Fingertip lesions	Digital tip ulcers Fingertip pitting scars	4
4. Telangiectasia		2
5. Abnormal nailfold capillaries		3
6. Pulmonary arterial HTN ± ILD (max score 2)	Pulmonary arterial HTN ILD	2
7. Raynaud's phenomenon		2
8. Scleroderma-related Ab	Anti-centromere Anti-topoisomerase I Anti-RNA polymerase III	2

* Score of ≥9 is sufficient to classify a patient as having definite scleroderma (sensitivity 0.95, specificity 0.93)

Epidemiology
- F:M=3-4:1, peaking in 5th decade
- associated with HLA-DR1 and environmental exposures (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)
- limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)

CREST Syndrome
Calcinosis
Raynaud's phenomenon
Esophageal dysmotility
Sclerodactyly
Telangiectasia

Scleroderma is the most common cause of secondary Raynaud's phenomenon

Cyclophosphamide vs. Mycophenolate Mofetil in Scleroderma Lung Disease
Lancet Respir Med 2016;4:708-719
Study: Double-blind, randomized, parallel group trial.
Purpose: To compare the toxicity and efficacy of cyclophosphamide vs. mycophenolate mofetil on lung function.
Results: In both treatment groups, the adjusted percent predicted FVC improved from baseline to 24 mo. Mycophenolate mofetil was associated with less toxicity and was better tolerated.
Conclusion: Treatment of SSc-ILD with mycophenolate mofetil for 2 yr or cyclophosphamide for 1 yr both result in improved lung function. However, mycophenolate mofetil is the current preference for treatment of SSc-ILD due to its better tolerability.

Raynaud's Phenomenon DDx
COLD HAND
Cryoglobulins/**C**ryofibrinogens
Obstruction/**O**ccupational
Lupus erythematosus, other connective tissue disease
DM/**D**rugs
Hematologic problems (polycythemia, leukemia, etc.)
Arterial problems (atherosclerosis)/
Anorexia nervosa
Neurologic problems (vascular tone)
Disease of unknown origin (idiopathic)

Clinical Presentation

Table 19. Clinical Manifestations of Scleroderma

System	Features
Dermatologic	Painless non-pitting edema → skin tightening Ulcerations, calcinosis, periungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias Characteristic face: mask-like facies with tight lips, beak nose, radial perioral furrows
Vascular	Raynaud's phenomenon → digital pits, gangrene Thrombosis
Gastrointestinal (~90%)	Distal esophageal hypomotility → dysphagia Loss of lower esophageal sphincter function → gastroesophageal reflux disease (GERD), ulcerations, strictures Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss Large bowel hypomotility → wide mouth diverticula are pathognomonic radiographic finding on barium study
Renal	Mild proteinuria, Cr elevation, HTN "Scleroderma renal crisis" (10-15%) may lead to malignant arterial HTN, oliguria, and microangiopathic hemolytic anemia
Pulmonary (~80%)	Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions
Cardiac	Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias
Musculoskeletal	Polyarthralgias "Resorption of distal tufts" (radiological finding) Proximal weakness 2° to disuse, atrophy, low grade myopathy, tendon friction rubs
Endocrine	Hypothyroidism

Features of Pathologic Raynaud's Syndrome

New onset

Asymmetric

Precipitated by stimuli other than cold or emotion

Associated with distal pulp pitting or tissue reabsorption

Digit ischemia

Capillary dilatation by capillaroscopy

Investigations

- blood work
  - CBC, Cr, ANA
  - anti-topoisomerase 1/anti-Scl-70 antibody: specific but not sensitive for diffuse systemic sclerosis
  - anti-centromere antibody: favours diagnosis of CREST (limited systemic sclerosis)
  - anti-RNA polymerase III antibody: associated with severe skin involvement, increased risk of renal crisis
- PFT
  - assess and monitor for ILD
- echocardiogram
  - rule out pulmonary HTN
- imaging
  - baseline CXR to rule out ILD

Treatment

- dermatologic
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), MTX (limited evidence)
- vascular
  - Raynaud's: keep hands and body warm, smoking cessation
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE2 inhibitors, PDE5 inhibitors), fluoxetine
- gastrointestinal
  - GERD: PPIs are first-line, then H2-receptor antagonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
  - motility disturbances: prokinetics
- renal disease
  - ACE inhibitor for hypertensive crisis
  - see Nephrology, NP36 for scleroderma renal crisis
- pulmonary
  - early interstitial disease: mycophenolate mofetil (less toxicity) or cyclophosphamide
  - pulmonary HTN: vasodilators (e.g. bosentan, epoprostenol, and PDE5 inhibitors)
  - rapidly progressive disease at risk of organ failure: consider hematopoietic stem cell transplantation
- cardiac
  - pericarditis: systemic steroids
- musculoskeletal
  - arthritis: NSAIDs
  - myositis: systemic steroids

Inflammatory Myopathy

Definition
- autoimmune diseases characterized by proximal muscle weakness ± pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process
- associated with malignancy
  - increased risk of malignancy: age >50, DMM > PM, elevated CK, peak incidence of malignancy at onset of myositis or within 1st yr, dysphagia, ulcerative skin lesions, cutaneous vasculitis, anti-P155/140 antibody
- associated with other CTDs, Raynaud's phenomenon, autoimmune disorders

Classification
- includes DMM, PM, NAM and IBM
- adult and juvenile forms
- newly characterized entities:
  - focal necrotizing myopathy (secondary to statin)
  - amyopathic myopathy (anti-synthetase syndrome, MDA-5 syndrome)

Inclusion Body Myositis
- age >50, M>F, slowly progressive, vacuoles in cells on biopsy
- patient unresponsive to treatment
- predominantly distal over proximal muscle weakness
- muscle biopsy positive for inclusion bodies

POLYMYOSITIS/DERMATOMYOSITIS

Definition
- PM and DMM are idiopathic inflammatory myopathies characterized by inflammation and proximal skeletal muscle weakness
- notably, DMM often presents with characteristic skin manifestations

Signs of DMM
Gottron's papules and Gottron's sign are pathognomonic of DMM (occur in 70% of patients)

Etiology and Pathophysiology
- PM is a T cell-mediated process with myocytes being the primary target, characterized by focal endomysial infiltrates (CD8+ T cells) surrounding muscle fibres, found in adults
- DMM is a complement mediated process with perivascular inflammatory infiltrates (CD4+ T cells > CD8+ T cells) leading to perifascicular atrophy of muscle fibres

Clinical Presentation
- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over wk to mo; difficulty lifting head off pillow, arising from chair, climbing stairs
- dermatological
  - DMM has characteristic dermatological features (F>M, children and adults)
    - Gottron's papules
      - pink-violaceous, flat-topped papules overlying the dorsal surface of the MCP and IP
    - Gottron's sign
      - erythematous, smooth or scaly patches over the extensor surface of elbows, knees, or medial malleoli
    - heliotrope rash: violaceous rash over the eyelids; usually with edema
    - shawl sign: poikilodermatous, erythematous rash over neck, upper chest, and shoulders
    - mechanic's hands: dry, crackled lesions on palmar and lateral surfaces of digits, especially over the pulp space, also seen in a subtype of myositis called anti-synthetase syndrome
    - periungual erythema
- cardiac
  - arrhythmias, congestive heart failure, conduction defect, ventricular hypertrophy, pericarditis
- gastrointestinal
  - oropharyngeal and lower esophageal dysphagia, reflux
- pulmonary
  - weakness of respiratory muscles, ILD, aspiration pneumonia

Malignancies Associated with DMM
- Breast
- Lung
- Colon
- Ovarian

Investigations
- general lab tests: CK, CBC, ESR and/or CRP, TSH
- serologic tests: ANA, anti-Jo-1 (DMM), anti-Mi-2, anti-SRP (usually not available at commercial labs)
- imaging: MRI may be used to localize biopsy site
- EMG: characteristic findings of muscle inflammation and damage
- muscle biopsy can aid in diagnosis, however not needed in those with classic skin findings and muscle weakness

Treatment
- non-pharmacological treatment
  - PT and OT, speech-language therapy for esophageal dysfunction
- pharmacological treatment
  - high-dose glucocorticoid (e.g. prednisone 1 mg/kg/d) usually not exceeding 80 mg daily and slow taper after patient improvement (~6 wk)
  - add immunosuppressive agents (azathioprine, MTX)
  - IVIG if severe or refractory muscle weakness, particularly when accompanied by dysphagia and/or dyspnea
  - hydroxychloroquine for DMM rash
- malignancy surveillance
  - detailed history and physical (breast, pelvic, and rectal exams)
  - CXR, abdominal and pelvic U/S, fecal occult blood, Pap test, mammogram ± CT scan (thoracic, abdominal, pelvic)

Sjögren's Syndrome

Definition
- autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca/xerophthalmia) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
- exists on a spectrum and may evolve into a systemic disorder (20%) with diminished exocrine gland activity and extraglandular features
- primary and secondary forms (associated with RA, SLE, DMM, and HIV)
- prevalence 0.5%, F>>M at 10:1, 40-60 yr
- increased risk of non-Hodgkin's lymphoma (lifetime incidence 6-7%)

Table 20. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for Primary Sjögren's Syndrome (at least 1 inclusion criteria, no condition in exclusion criteria, score ≥4)

Criteria	Score	Comments
Labial salivary gland biopsy with focal lymphocytic sialadenitis with focus score ≥1 focus/4mm^2	3	Focus scores are histopathologic grading systems Strongly associated with phenotypic ocular and serological components of Sjögren's
Anti-SSA- or Ro-positive	3	
Ocular staining score ≥5 (or van Bijsterveld score ≥4 on at least one eye)	1	Ocular staining score based on fluorescein dye examination of conjunctiva and cornea to determine clinical changes
Schirmer's test ≤5 mm/5 min on at least one eye	1	
Unstimulated whole saliva flow rate ≤0.1 mL/min	1	
Inclusion criteria (positive response to at least one question): 1) Have you had daily, persistent, troublesome dry eyes for more than 3 mo? 2) Do you have a recurrent sensation of sand or gravel in the eyes? 3) Do you use tear substitutes more than 3 times a d? 4) Have you had a daily feeling of dry mouth for more than 3 mo? 5) Do you frequently drink liquids to aid in swallowing dry food?		
Exclusion criteria include prior diagnosis of any of the following conditions: 1) History of head and neck radiation treatment, 2) Active hepatitis C infection (with confirmation by polymerase chain reaction, 3) AIDS, 4) Sarcoidosis, 5) Amyloidosis, 6) Graft-versus-host disease, 7) IgG4-related disease		

Arthritis Rheumatol. 2017;69:35-45

Clinical Presentation
- "sicca complex": dry eyes (keratoconjunctivitis sicca/xerophthalmia), dry mouth (xerostomia), complicated by staphylococcal blepharitis
- dental caries, oral candidiasis, angular cheilitis (inflammation and fissuring at the labial commissures of the mouth)
- extraglandular manifestations
  - fatigue, low-grade fever
  - autoimmune thyroid dysfunction
  - arthralgias, arthritis
  - subclinical diffuse ILD, xerotrachea leading to chronic dry cough
  - renal disease, glomerulonephritis
  - palpable purpura, vasculitis
  - peripheral neuropathy
  - lymphoma risk greatly increased

Classic Triad (identifies 93% of Sjögren's patients)

Dry eyes

Dry mouth (xerostomia) → dysphagia

Arthritis (small joint, asymmetrical, non-erosive) but may be associated with rheumatoid arthritis, in which case, the arthritis is erosive and symmetric

Treatment
- ocular
  - artificial tears/tear gel if severe, moisture retaining eyewear, humidifiers, or surgical punctal occlusion for dry eyes
- oral
  - good dental hygiene, hydration
  - avoid alcohol and tobacco
  - parasympathomimetic agents that stimulate salivary flow (e.g. pilocarpine)
  - topical nystatin or clotrimazole x4-6 wk for oral candidiasis
- systemic treatments (e.g. hydroxychloroquine, corticosteroids) are ineffective, rituximab can be used in severe organ-threatening disease (e.g. vasculitis)

Mixed Connective Tissue Disease

Definition
- syndrome with features of 3 different CTDs (e.g. SLE, scleroderma, myositis)
- common symptoms: Raynaud's phenomenon, swollen fingers

Investigations
- blood work: anti-RNP (see *Table 12, RH8*)

Treatment
- treatment is generally guided by the severity of symptoms and organ system involvement

Prognosis
- prognosis is variable: some individuals go into remission, others develop a distinct connective tissue disease (e.g. SLE, SSc), and others develop a severe disease course
  - pulmonary arterial HTN is a major cause of death

Overlap Syndrome

Definition
- syndrome with sufficient diagnostic features of 2+ different CTDs

Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction of any organ system
- diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection; constitutional symptoms such as fever, weight loss, anorexia, fatigue
  - labs non-specific: anemia, increased WBC and CRP, abnormal U/A
  - investigations: biopsy if tissue accessible; angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressive agents

Table 21. Classification of Vasculitis and Characteristic Features

Classification	Characteristic Features
SMALL VESSEL	
Non-ANCA-associated	Immune complex-mediated (most common mechanism)
Anti-GBM (Goodpasture's disease)	Autoantibodies targeting type IV collagen in both glomerular basement membrane and alveoli causing glomerulonephritis and/or pulmonary findings
Anti-C1q vasculitis (hypocomplementemic urticarial vasculitis syndrome)	Specific autoimmune disorder with at least 6 mo of urticaria with C1q complement deficiency with various systemic findings
Predominantly cutaneous vasculitis	Also known as hypersensitivity/leukocytoclastic vasculitis
IgA vasculitis (formerly Henoch-Schönlein purpura (HSP)) (see Pediatrics, P98)	Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting; most common in childhood
Cryoglobulinemic vasculitis (CV)	Systemic vasculitis caused by circulating cryoproteins forming immune complexes; 60-80% of cases are due to hepatitis C, 5-10% are due to a CTD (SLE, RA, SS), 5-10% are due to a lymphoproliferative disorder, and the remaining 5-10% are idiopathic or "essential." CV may be associated with underlying infection (e.g. hepatitis C) or CTD
ANCA-associated (i.e. PR3-ANCA) Granulomatosis with polyangiitis (GPA, formerly Wegener's) PR3 (c-ANCA) > MPO (p-ANCA)	Granulomatous inflammation of vessels of respiratory tract and kidneys leading to pulmonary hemorrhage and glomerulonephritis; initially may have upper respiratory tract infection (URTI) symptoms (sinusitis); most common in middle age
EGPA, formerly Churg-Strauss syndrome (50% ANCA positive)	Granulomatous inflammation of vessels with hypereosinophilia and eosinophilic tissue infiltration, frequent lung involvement (asthma, allergic rhinitis), associated with MPO-ANCA in 40-50% of cases. Other manifestations include peripheral neuropathy (70%), GI involvement, myocarditis, and rarely coronary arteritis; average age 40s
Microangiopathic polyangiitis (MPA) (70% ANCA positive, usually MPO)	Pauci-immune necrotizing vasculitis, affects kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), and skin; most common in older age
MEDIUM VESSEL	
PAN	Segmental, non-granulomatous necrotizing inflammation Unknown etiology in most cases, any age (average 40-50s), M>F
Kawasaki disease (see Pediatrics, P99)	Arteritis and mucocutaneous lymph node syndrome

Features of Small Vessel Vasculitis
- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers (erosions)

c-ANCA (e.g. PR3-ANCA): cytoplasmic anti-neutrophil cytoplasmic Ab associated with anti-PR3

p-ANCA (e.g. MPO-ANCA): perinuclear anti-neutrophil cytoplasmic Ab associated with multiple antigens, e.g. MPO, lactoferrin (IBD), cathepsin, elastase, etc. Of these, only antibodies to MPO have been associated with the development of vasculitis

EGPA Triad
- Allergic rhinitis and asthma (often quiescent at time of vasculitis)
- Eosinophilic infiltrative disease resembling pneumonia
- Systemic vasculitis often mononeuritis multiplex/peripheral neuropathy and peripheral eosinophilia

Features of Medium Vessel Vasculitis
- Livedo reticularis
- Erythema nodosum
- Raynaud's phenomenon
- Nodules
- Digital infarcts
- Ulcers

Table 21. Classification of Vasculitis and Characteristic Features

Classification	Characteristic Features
LARGE VESSEL	
GCA/Temporal arteritis	Inflammation predominantly of the aorta and its branches Ages >50, F>M Temporal H/A, jaw claudication, scalp tenderness, vision loss
Takayasu's arteritis	"Pulseless disease," unequal peripheral pulses, chronic inflammation, most often the aorta and its branches Most common in young adults of Asian descent, ages 10-40, F>M, risk of aortic aneurysm
OTHER VASCULITIDES	
Buerger's disease ("Thromboangiitis Obliterans")	Inflammation and clotting of small and medium-sized arteries and veins of distal extremities, may lead to distal claudication and gangrene, the most important etiologic factor is cigarette smoking. Most common in young Asian males, M>F
Behçet's disease	Multi-system disorder presenting with ocular involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement Most common in Mediterranean and Asian populations, average age 30 y/o, M>F
Vasculitis mimicry (i.e. pseudovasculitis)	Cholesterol emboli, atrial myxoma, subacute bacterial endocarditis (SBE), APS

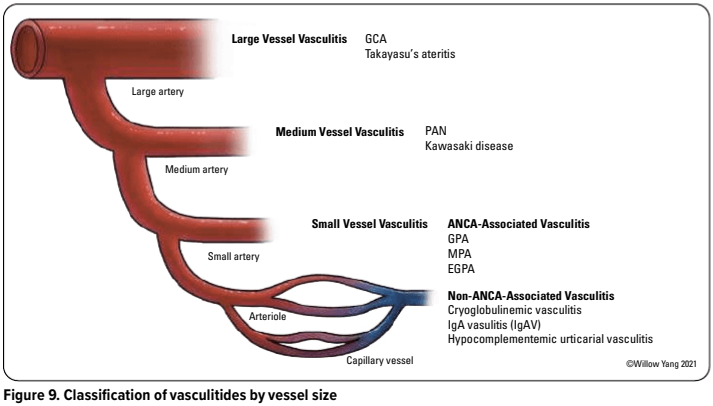

Figure 9. Classification of vasculitides by vessel size
J. C. Jennette, R. J. Falk, P. A. Bacon, et al, Arthritis & Rheumatology (65, 1), p. 1, copyright © 2020, Modified by Permission of John Wiley and Sons

Small Vessel Non-ANCA-Associated Vasculitis

CUTANEOUS VASCULITIS

- subdivided into:
  - drug-induced vasculitis
  - vasculitis associated with other underlying primary diseases (CTD, IBD, infections, malignancies – hematologic > solid tumours)
  - idiopathic

Etiology and Pathophysiology

- cutaneous vasculitis following:
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes
- small vessels involved (post-capillary venules most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Clinical Presentation

- palpable purpura (usually on lower extremities) ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules
  - renal or joint involvement may occur, especially in children

Investigations

- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment
- stop possible offending drug; treat underlying primary disease
- NSAIDs, low-dose corticosteroids
  - immunosuppressive agents in resistant cases
- usually self-limiting, but in ⅓ of cases, it may recur

Small Vessel ANCA-Associated Vasculitis

GRANULOMATOSIS WITH POLYANGIITIS (GPA, formerly known as Wegener's Granulomatosis)

Definition
- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates caused by pulmonary hemorrhage), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA by indirect immunofluorescence (IIF) and PR3-ANCA by ELISA; however, changes in ANCA levels do not predict remission or relapse
- incidence: 2-3 in 100,000; more common in Northern latitudes

Table 22. Classification Criteria for GPA*

Clinical Criteria		Score
Criteria	**Description**	
Nasal involvement	Crusting, ulcers, epistaxis, congestion, blockage, or septal defect/perforation	+3
Cartilaginous involvement	Ear/nose cartilage inflammation, hoarseness or stridor, endobronchial involvement, or saddle nose deformity	+2
Hearing loss	Conductive or sensorineural	+1
Laboratory, Imaging, and Biopsy Criteria		
c-ANCA or anti-PR3-positive		+5
Pulmonary nodules, mass, or cavitation on chest imaging		+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy		+2
Inflammation, consolidation, or effusion of nasal/paranasal sinuses, or mastoiditis on imaging		+1
Pauci-immune glomerulonephritis on biopsy		+1
p-ANCA or anti-MPO-positive		-1
Blood eosinophil count >1x10⁹/L		-4

*Diagnosed if ≥5
American College of Rheumatology, 2022

Etiology and Pathophysiology
- pathogenesis depends on genetic susceptibility and environmental triggers (e.g. infection)
  - dysregulated immune response due to loss of B and T cell tolerance
  - acute vascular injury mediated by neutrophils and monocytes

Clinical Presentation
- systemic
  - malaise, fever, weakness, weight loss
- head, eyes, ears, nose, and throat (HEENT)
  - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
  - proptosis due to: inflammation/vasculitis involving extraocular muscles, granulomatous retrobulbar space-occupying lesions or direct extension of masses from the upper respiratory tract
  - hearing loss due to involvement of cranial nerve (CN) VIII
- pulmonary
  - cough, hemoptysis, granulomatous upper respiratory tract masses, tracheal and bronchial stenosis
- renal
  - hematuria, proteinuria, elevated Cr, glomerulonephritis
- other
  - joint, skin, eye complaints-iritis, vasculitic neuropathy

Investigations
- blood work: anemia (normocytic), increased WBC, increased Cr, increased CRP, elevated platelet count, ANCA (PR3 > MPO)
- urinalysis: proteinuria, hematuria, RBC casts
- CXR/CT: pneumonitis, lung nodules, infiltrations, cavitary lesions
- biopsy for confirmation of disease: skin, renal (segmental necrotizing glomerulonephritis), lung (vasculitis, necrosis)
- CRP may be used to monitor response to treatment in some patients

Classic Features of GPA
Necrotizing granulomatous vasculitis of lower and upper respiratory tract

Focal segmental glomerulonephritis

See *Landmark Rheumatology Trials RH34* for more information on the RAVE trial. It examined the efficacy of rituximab for the induction and maintenance of remission in patients with ANCA-associated Vasculitides.

See *Landmark Rheumatology Trials RH34* for more information on the MAINRITSAN3 trial. It examined the efficacy of extended maintenance rituximab in patients with ANCA-associated Vasculitides

Treatment
- severe, life or organ-threatening disease
  - induction therapy: IV glucocorticoids + either IV or oral cyclophosphamide OR rituximab
  - glucocorticoid: methylprednisolone 0.5-1.0 g/d IV x1-3 d followed by prednisone 1 mg/kg/d PO x2-4 wk and then gradual taper
  - cyclophosphamide: 2 mg/kg/d (max 200 mg/d) PO for maximum of 3-6 mo OR 15 mg/kg IV (max 1200 mg) every 2 wk for 3 doses, then every 3 wk for 3-6 doses (dose adjust for older age and renal failure)
  - rituximab: 375 mg/m ^{2}x4 weekly infusions or 1 g IV x 2 doses 14 d apart
  - maintenance therapy: initiated once remission is achieved, consider corticosteroid-sparing agents such as rituximab for maintenance, azathioprine, MTX, and mycophenolate are reasonable alternatives
- plasma exchange can be an adjunct treatment for patients with severe organ involvement (renal failure, pulmonary hemorrhage) not responding to conventional induction treatment
- non-organ-threatening disease
  - prednisone 0.5-1 mg/kg/d PO and MTX 15-25 mg PO/SC weekly OR azathioprine 2 mg/kg/d
- screening and prophylaxis
  - all patients should receive screening and prophylaxis for corticosteroid-induced osteoporosis, PUD prevention, and Pneumocystis jiroveci prophylaxis (trimethoprim/sulfamethoxazole 160/800 mg PO 3x/wk)

Medium Vessel Vasculitis

POLYARTERITIS NODOSA

Definition
- systemic, necrotizing vasculitis of medium-sized vessels, defined as visceral arteries and their branches
- ANCA-negative, classically lung-sparing
- 5-10% associated with hepatitis B positivity
- incidence: 0.7 in 100,000; affects individuals between 40-60 yr; M:F=2:1

Table 23. Classification Criteria for PAN*

Criteria	Description
1. Weight loss	≥4 kg, not due to dieting or other factors
2. Myalgias, weakness, or leg tenderness	Diffuse myalgias or muscle weakness
3. Livedo reticularis	Mottled, reticular pattern over skin
4. Neuropathy	Mononeuropathy, mononeuropathy multiplex, or polyneuropathy
5. Testicular pain or tenderness	Not due to infection, trauma, or other causes
6. dBP >90 mmHg	Development of HTN with dBP >90 mmHg
7. Elevated Cr or BUN	Cr >130 µmol/L (1.5 mg/dL), BUN >14.3 mmol/L (40 mg/dL)
8. Hepatitis B positive	Presence of hepatitis B surface antigen or Ab
9. Arteriographic abnormality	Commonly aneurysms
10. Biopsy of artery	Presence of granulocytes and/or mononuclear leukocytes in the artery wall

*Diagnosed if 3 or more of the above 10 criteria present
American College of Rheumatology, 1990

Etiology and Pathophysiology
- focal pan-mural necrotizing vasculitis in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion

Clinical Presentation
- systemic: fatigue, weight loss, weakness, fever, arthralgias
- dermatologic: livedo reticularis, nodules, purpura, eruptions
- renal: renal insufficiency leading to HTN
- neurologic: mononeuropathy multiplex in both motor and sensory nerves
- abdominal: abdominal pain, mesenteric arteritis

Investigations
- blood work: CBC, CRP, Cr, BUN, urinalysis, liver enzymes, p-ANCA, hepatitis B and C serology
- imaging: CT or MRI angiography shows beading appearance of blood vessels seen
- biopsy of affected organ (e.g. skin, nerve); biopsy of highly vascular tissues (e.g. liver) not recommended due to risk of aneurysm rupture

Treatment
- PAN with no major organ manifestations
  - glucocorticoids ± azathioprine
- PAN with major organ manifestations (CNS, cardiac, GI, renal)
  - induction therapy with high-dose glucocorticoids + cyclophosphamide for 3-6 mo followed by maintenance therapy with low-dose prednisone and either azathioprine, MTX, or leflunomide
  - treatment should be a minimum of 18 mo
- hepatitis B virus-associated vasculitis
  - prednisone 1 mg/kg/d PO x7 d (then taper and withdraw by 14 d) ± methylprednisolone 15 mg/kg/d IV x1-3 d
  - after corticosteroid therapy, treat with plasma exchange + antiviral therapy

Large Vessel Vasculitis

GIANT CELL ARTERITIS/TEMPORAL ARTERITIS

Table 24. Classification Criteria for GCA*

Absolute Requirement	
Age at onset ≥50	
Additional Clinical Criteria	**Score**
Morning stiffness in shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery	+2
Laboratory, Imaging, and Biopsy Criteria	
Maximum ESR ≥50 mm/h or maximum CRP ≥ 10 mg/liter	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5
Bilateral axillary involvement	+2
FDG-PET activity throughout aorta +2	

*Sum the scores for 10 items, if present. A score of ≥ 6 points is needed for the classification of GCA. American College of Rheumatology, 2022

GCA Criteria
Cumulative score of ≥6 points yields sensitivity of 87%, specificity of 95%

Epidemiology
- most common vasculitis in North America
- patients >50 yr; peak incidence 70-80 yr
- F:M=2:1
- north-south gradient (predominance in Northern Europe and US)
- affects extracranial arteries

Clinical Presentation
- new onset temporal H/A ± scalp tenderness overlying temporal artery
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
- tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
- PMR (proximal shoulder/pelvic girdle pain and stiffness, constitutional symptoms, elevated ESR) is the most common extracranial symptom
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta resulting in pulseless disease), aortic aneurysm ± rupture are late complications
- constitutional symptoms (e.g. fever of unknown origin in patients ≥65 yr)

Medical Emergency
If untreated, GCA can lead to permanent blindness in 20-25% of patients
Treat on clinical suspicion

Investigations
- diagnosis made by clinical suspicion, increased ESR, or CRP, and either imaging (colour Doppler U/S of temporal ± axillary arteries (+ halo sign), MRI of temporal vessel, PET scan showing inflammation throughout aorta) or a positive temporal artery biopsy

Treatment
- if suspect GCA, immediately start high-dose prednisone 1 mg/kg PO in divided doses for 2-4 wk, and then taper prednisone by 10 mg per 1-2 wk as symptoms resolve; highly effective in treatment and prevention of blindness and other vascular complications
- consider low-dose ASA if there is critical involvement of the vertebral or carotid arteries
- if presenting with vision loss at diagnosis, methylprednisolone 1000 mg/d IV for 3 d followed by high-dose prednisone 1 mg/kg/d PO in divided doses with taper
- tocilizumab, an IL-6 receptor monoclonal Ab, has also been used in combination with glucocorticoids to treat GCA (new or relapsing)

Prognosis
- increased risk of thoracic aortic aneurysm and aortic dissection
- yearly CXR ± abdominal U/S as screening

Seronegative Rheumatic Disease

Table 25. A Comparison of the Spondyloarthropathies

Feature	AS	PsA	ReA	EA
M:F	3:1	1:1	8:1	1:1
Age of Onset	20s	35-45	20s	Any
Peripheral Arthritis	25%	96%	90%	Common
Distribution	Axial, large joints	Any	LE*	LE*
Sacroiliitis	100%	40%	80%	20%
Dactylitis	Uncommon	Common	Occasional	Uncommon
Enthesitis	Common	Common	Common	Less Common
Skin Lesions	Rare	100% Eventually psoriasis, 70% at onset of arthritis	Occasional Keratoderma blennorrhagica	Occasional Pyoderma, erythema nodosum
Uveitis	Common	Occasional	20%	Rare
Urethritis	Rare	Uncommon	Common	Rare
HLA-B27	90-95%	40%	80%	30%

*LE = lower extremities

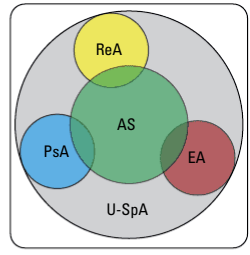

Figure 10. Spondyloarthropathy subsets

AS shares some features with the other three types of seronegative spondyloarthropathies such as ReA, EA, PsA, and U-sPA

Ankylosing Spondylitis

Definition

- chronic inflammatory arthritis involving the SI joints and vertebrae
- enthesitis is a major feature (e.g. Achilles tendinitis, plantar fasciitis)
- prototypical spondyloarthropathy

Table 26. ASAS Classification Criteria for Axial Spondyloarthritis*

1. Back pain of any type for at least 3 mo and age of onset <45 yr
2. Sacroiliitis on imaging plus ≥1 AS feature or HLA-B27 positive plus ≥2 AS features

AS Features	Sacroiliitis on Imaging
HLA-B27 positive	Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with AS
Inflammatory back pain	OR
Arthritis	Definite radiographic sacroiliitis ≥grade 2 bilaterally or grade 3-4 unilaterally
Enthesitis (heel)	
Uveitis	
Dactylitis	
Psoriasis	
Crohn's disease/colitis	
Good response to NSAIDs	
FMHx of SpA	
Elevated CRP	

*Spondylarthropathy: inflammatory joint disease of the vertebral column

Consider AS in the differential for causes of aortic regurgitation

Etiology and Pathophysiology

- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

Epidemiology

- M:F=3:1; females have milder disease (may be under-diagnosed), more peripheral arthritis, and upper spine spondylitis
- 90-95% of patients are HLA-B27 positive (9% of the general population is HLA-B27 positive)

Rule of 2s
AS occurs in
0.2% of the general population
2% of HLA-B27 positive individuals
20% of HLA-B27 positive individuals with affected family member

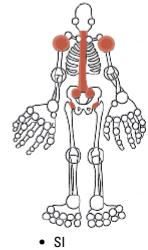

Figure 11. Common sites of involvement of AS

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
Self-reported scoring system that focuses on fatigue, axial pain, peripheral pain, enthesitis, and morning stiffness

Table 27. Types of Back Pain

Parameter	Mechanical	Inflammatory
Past History	±	++
Family History	–	+
Onset	Acute	Insidious
Age	15-90 yr	<45 yr
Sleep Disturbance	±	++ (worse during 2nd half of night)
Morning Stiffness	<30 min	>1 h
Involvement of Other Systems	–	+
Exercise	Worse	Better
Rest	Better	Worse
NSAID Responsiveness	±	++
Radiation of Pain	Anatomic (L5-S1)	Diffuse (thoracic, buttock)
Sensory Symptoms	+	–
Motor Symptoms	+	–

Clinical Presentation

- **axial**
  - mid and lower back stiffness, morning stiffness >1 h, night pain, alternating buttock pain, painful SI joint (+ FABER test)
  - spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion, normal >5 cm at T4), cervical (global decrease, often extension first)
  - postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance (>5 cm)
- **peripheral**
  - asymmetrical large joint arthritis, most often involving lower limb
  - enthesitis: tenderness over tibial tuberosity, or Achilles tendon and plantar fascia insertions into the calcaneus
  - dactylitis: toes or fingers
- **extra-articular manifestations**
  - ophthalmic: acute anterior uveitis is common (25-30% patients)
  - renal: amyloidosis (late and rare), IgA nephropathy
  - gastrointestinal: IBD
  - cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
  - respiratory: apical fibrosis (rare)
  - neurologic: cauda equina syndrome (rare)
  - skin: psoriasis

Investigations

- x-ray of SI joint: "pseudowidening" of joint due to erosion with joint sclerosis → bony fusion (late), symmetric sacroiliitis
- x-ray of spine: "squaring of edges" from erosion and sclerosis on corners of vertebral bodies (shiny corner sign) leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes) → "bamboo spine" radiographically
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes. Best seen on T2 short tau inversion recovery (STIR) images (suppress fat and see bone edema)
- labs: CBC, elevated ESR/CRP, ALP, Ca2+, serum protein electrophoresis (SPEP), BMD, HLA-B27

Treatment

- non-pharmacological therapy
  - prevent fusion from poor posture and disability through: exercise (e.g. swimming), postural and deep breathing exercises, outpatient PT, and smoking cessation
- pharmacological therapy
  - NSAIDs (first line of treatment for peripheral and axial disease)
  - glucocorticoids (topical eye drops, local injections, occasionally require systemic steroids prior to other effective Rx)
  - DMARDs only for peripheral arthritis (SSZ, MTX)
  - if inadequate response to two NSAIDs (or DMARD for peripheral arthritis only), consider anti-TNF agents or anti-IL-17 for axial and peripheral involvement
  - manage extra-articular manifestations
- surgical therapy
  - hip replacement and vertebral osteotomy for marked deformity (latter rarely performed)

Prognosis

- spontaneous remissions and relapses are common and can occur at any age
- function may be excellent despite spinal deformity
- favourable prognosis if female and age of onset >40 yr
- early onset with hip disease may lead to severe disability; may require arthroplasty

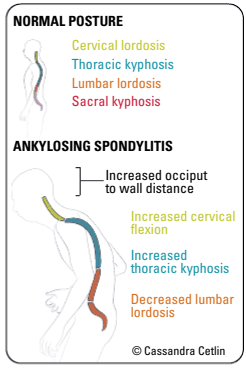

Figure 12. AS postural change

FABER (Flexion, ABduction, and External Rotation) Test
Passively flex, abduct, then gently externally rotate the leg. If pain is elicited during this movement, the location of the pain may help determine the location of the patient's pathology (e.g. hip joint, SI joint). However, it is poorly reproducible and inaccurate in discerning inflammatory vs. mechanical back pain

Modified Schöber Test

Patient must be standing erect with normal posture

Mark an imaginary horizontal line connecting both posterior superior iliac spines (close to the dimples of Venus)

A mark is placed 10 cm above this horizontal line, and another 5 cm below

The patient bends forward maximally: measure the difference between these two points

Report the increase (in cm to the nearest 0.1 cm)

The better of two tries is recorded

Extra-Articular Manifestations of AS

5 As
Anterior uveitis
Apical lung fibrosis
Aortic incompetence
Amyloidosis (kidneys)
Autoimmune bowel disease (ulcerative colitis)

Enteropathic Arthritis

Definition
- see Gastroenterology, *Inflammatory Bowel Disease*, G22

Clinical Presentation
- MSK manifestations in the setting of either ulcerative colitis (UC) or Crohn's disease (CD) including peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthropathy
- non-arthritic MSK manifestations can occur secondary to steroid treatment of bowel inflammation (arthralgia, myalgia, osteoporosis, AVN)

Both AS and EA feature symmetric sacroiliitis

Table 28. Comparing Features of Spondylitis vs. Peripheral Arthritis in EA

Parameter	Spondylitis	Peripheral Arthritis
HLA-B27 Association	Yes	No
Gender	M>F	M=F
Onset Before IBD	Yes	No
Parallels IBD Course	No	Yes
Type of IBD	UC=CD	CD
Treatment	NSAIDs (use cautiously, may exacerbate bowel disease); TNF inhibitors if resistant	NSAIDs, DMARDs; TNF inhibitors if resistant

Psoriatic Arthritis

Definition
- arthritic inflammation associated with cutaneous psoriasis, which may proceed (85%) or follow (15%) the arthritis
- seronegative rheumatic disease classified as a spondyloarthropathy

Etiology and Pathophysiology
- unclear but many genetic, immunologic, and some environmental factors involved (e.g. bacterial, viral, and trauma)
- low HLA-B27+ prevalence unless spondylitis is present (vs. 90% in AS)

Epidemiology
- psoriasis affects 1-2% of the population, of which 10-30% develop an arthropathy
- M:F=1:1

Clinical Presentation
- **dermatologic**
  - psoriasis: well-demarcated erythematous plaques with silvery scale
  - psoriatic nail changes (potential predictor for PsA): pitting, transverse or longitudinal ridging, discolouration, subungual hyperkeratosis, onycholysis, and oil drops
- **musculoskeletal**
  - 5 common arthritis patterns
    - asymmetric oligoarthritis (<5 small and/or large joints affected in asymmetric distribution; most common – 70%)
    - arthritis of DIPs (nail changes are more common)
    - symmetric polyarthritis (similar to RA)
    - asymmetric sacroiliitis and spondylitis (usually older, male patients)
    - arthritis mutilans (destructive and deforming small joint polyarthritis)
  - other findings: dactylitis, enthesopathy, morning stiffness >30 min (50%)
- **ophthalmic**
  - conjunctivitis, iritis (anterior uveitis)
- **cardiac and respiratory** (late findings)
  - aortic insufficiency
  - apical lung fibrosis
- **neurologic**
  - cauda equina syndrome
- **radiologic**
  - floating syndesmophytes
  - pencil-in-cup appearance at IPs
  - osteolysis, periostitis

Check "hidden" areas for psoriatic lesions (ears, hairline, umbilicus, gluteal cleft, nails)
TNF inhibitors are effective treatments for PsA with no important added risks associated with their short-term use

Table 29. CASPAR Criteria for PsA*

Criterion	Description
1. Evidence of psoriasis	Current (2 points), past (1 point), or family history (1 point)
2. Psoriatic nail dystrophy (1 point)	Onycholysis, pitting, hyperkeratosis
3. Negative results for RF (1 point)	Preferably by ELISA, nephelometry
4. Dactylitis (1 point)	Current or past history
5. Radiological evidence (1 point)	Juxta-articular bone formation on hand or foot x-rays

*To meet the CASPAR (CIASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the above 5 categories.
Arthritis Rheum 2006 Aug;54(8):2665-2673. Classification criteria for PsA development

Treatment
- treat skin lesions (e.g. steroid cream, salicylic and/or retinoic acid, tar, UV light)
- NSAIDs and/or IA steroids (as an adjuvant), benefit should be seen within a few wk, should not be the sole therapy >3 mo
- DMARDs to minimize erosive disease (use early in peripheral joint involvement)
  - non-biologic DMARDs (MTX, SSZ, or leflunomide)
  - biologic therapies include anti-TNF agents, anti-IL-17 (secukinumab), and anti-IL-12/23 (ustekinumab), Jak inhibitors

Reactive Arthritis

Definition
- seronegative spondyloarthropathy in which patients have a peripheral arthritis and one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tract
- this term should not be confused with rheumatic fever or viral arthritides

Clinical Triad of Reactive Arthritis
Arthritis
Conjunctivitis/uveitis
Urethritis/cervicitis

"Can't See, Can't Pee, Can't Climb a Tree"
Triad of conjunctivitis, urethritis, and arthritis is 99% specific (but 51% sensitive) for ReA

Etiology
- onset following an infectious episode either involving the GI or GU tract
  - GI: *Shigella, Salmonella, Campylobacter, Yersinia, C. difficile* species
  - GU: *Chlamydia* (isolated in 16-44% of ReA cases), *Mycoplasma* species
- acute clinical course
  - onset 1-4 wk post-infection
  - lasts wk to mo
  - often recurring
  - spinal involvement persists

Epidemiology
- more common in ages 20-40
- M>F if GU associated, M=F if GI associated
- in HLA-B27+ patients, axial > peripheral involvement

Clinical Presentation
- **musculoskeletal**
  - asymmetric peripheral arthritis, spondylitis/sacroiliitis, enthesitis (Achilles tendinitis, plantar fasciitis), dactylitis
- **ophthalmic**
  - iritis (anterior uveitis), conjunctivitis
- **dermatologic**
  - keratoderma blennorrhagicum (hyperkeratotic skin lesions on palms and soles) and balanitis circinata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- **gastrointestinal**
  - oral ulcers, diarrhea
- **genitourinary**
  - urethritis, prostatitis, cervicitis, cystitis, sterile pyuria; presence not related to site of initiating infection

Investigations
- diagnosis is clinical plus laboratory
- evidence of antecedent or concomitant infection (stool culture, urine, and genital swab testing)
- blood work: normocytic, normochromic anemia, and leukocytosis
- sterile cultures
- serology: HLA-B27 positive, elevated ESR/CRP

Treatment
- antibiotics for non-articular infections
- NSAIDs (naproxen 500 mg BID/TID, diclofenac 50 mg TID, indomethacin 50 mg TID/QID), PT, exercise

- local therapy
  - IA steroid injection (triamcinolone acetonide)
  - topical steroid for ocular involvement
- systemic therapy
  - corticosteroids (starting dose 20 mg/d)
  - DMARDs (for refractory ReA with peripheral joint involvement only) (SSZ, MTX)
  - TNF-α inhibitors for spinal inflammation (for disease refractory to NSAIDs, DMARDs)

Prognosis
- self-limited, typically 3-5 mo, varies based on pathogen and patient's genetic background
- chronic in 15-20% of cases

Crystal-Induced Arthropathies

Table 30. Gout vs. Pseudogout

Parameter	Gout	Pseudogout
Gender	M>F	M=F
Age	Middle-aged males Post-menopausal females	Usually elderly
Onset of Disease	Acute Can become chronic if high uric acid untreated, people with renal failure, kidney transplant	Acute Chondrocalcinosis is asymptomatic but the clinical feature is generally acute
Crystal Type	Monosodium urate Negative birefringence (yellow when parallel to compensator filter), needle-shaped	CPPD Positive birefringence (blue when parallel), rhomboid-shaped
Distribution	First MTP classically; also midfoot, ankle, knee, or polyarticular	Knee, wrist; monoarticular, or polyarticular if chronic
Radiology (note findings are nonspecific)	Erosions	Chondrocalcinosis OA (knee, wrist, 2nd and 3rd MCP)
Treatment	Acute: NSAIDs, corticosteroids, colchicine Chronic: ± allopurinol, febuxostat	NSAIDs, corticosteroids

Gout

Definition
- derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

Etiology and Pathophysiology
- uric acid can be obtained from the diet or made endogenously by xanthine oxidase, which converts xanthine to uric acid
- an excess of uric acid results in hyperuricemia
- uric acid can deposit in the skin/subcutaneous tissues (tophi), synovium (microtophi), and kidney, where it can crystalize to form monosodium urate crystals that lead to gout
- non-modifiable risk factors include: genetic mutations, male gender, and advanced age
- modifiable risk factors include: diet (alcohol, purine rich foods such as meats and seafoods, fructose/sugar sweetened foods; see list of precipitants below)
- other risk factors: renal failure, metabolic syndrome, dehydration (e.g. diuretics)

Clinical Presentation
- single episode progressing to recurrent episodes of acute inflammatory arthritis
- **acute gouty arthritis**
  - severe pain, erythema, joint swelling, usually involving lower extremities
  - joint mobility may be limited
  - attack will subside spontaneously within d to wk (5-10 d); may recur
- **tophi**
  - urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
  - common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
- **kidney**
  - gouty nephropathy
  - uric acid nephrolithiasis

Investigations
- joint aspirate: >90% of joint aspirates show crystals of monosodium urate (negatively birefringent, needle-shaped) if done early in course of presentation
- x-rays may show tophi as soft tissue swelling, bone/joints - punched-out lesions, erosion with "over-hanging" edge
  - U/S shows double-contour sign

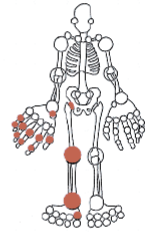

Figure 13. Common sites of involvement of gout (asymmetric joint involvement)

An acute gout attack may mimic cellulitis; however, joint mobility is usually preserved in cellulitis unless it overlaps a joint

Precipitants of Gout

Drugs are FACT
Furosemide
Aspirin® (low-dose)/**A**lcohol
Cyclosporine
Thiazide diuretics

Foods are SALT
Seafood
Alcohol (beer and spirits)
Liver and kidney
Turkey (meat)

2020 American College of Rheumatology Guideline for the Management of Gout
Arthritis Rheumatol 2020;72:879-95
- Initiate urate lowering therapy (ULT) for patients with:
  - ≥1 SC tophi
  - Radiographic damage attributable to gout
  - Frequent gout flares (≥2/yr)
- Allopurinol is preferred over all other ULTs as a first-line agent for all patients (including CKD stage ≥3)
- Initiate concomitant anti-inflammatory prophylaxis (e.g. colchicine, NSAIDs, prednisone/prednisolone) for 3-6 mo
- Continue ULT to target and maintain serum urate <6 mg/dL
- In patients with frequent gout flares or nonresolving SC tophi who have failed to achieve serum urate <6 mg/dL on uricosurics, xanthine oxidase inhibitors, and other interventions, pegloticase should be initiated and the current ULT should be discontinued
- Gout flares should be managed with NSAIDs, low-dose colchicine, or glucocorticoids as first-line agents

Treatment
- **acute gout**
  - NSAIDs: high-dose, then taper as symptoms improve
  - ice, rest and elevation of the affected limb
  - corticosteroids: IA (preferred), PO, or IM (if renal, cardiovascular, or GI disease and/or if NSAIDs contraindicated or failed). IV for patients with multiple joints flaring, unable to take oral medication, and already have IV line
  - colchicine: greatest benefit if used within the first 12-24 h. 1.2 mg at the first signs of an attack followed by 0.6 mg 1 h later and 0.6 mg BID on subsequent days until the attack has resolved. Caution in renal failure and/or older adults
- **chronic gout**
  - conservative
    - avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
    - avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, low dose ASA, cyclosporine)
    - additional management of lifestyle factors: limiting alcohol intake, limiting high-fructose corn syrup, for overweight/obese patients weight loss is recommended (regardless of activity level)
  - medical
    - antihyperuricemic drugs first line: allopurinol (not nephrotoxic), second line: febuxostat. Both decrease uric acid production by inhibiting xanthine oxidase. Start low and titrate up. Do not use febuxostat if history of cardiovascular disease
    - uricosuric drugs (probenecid, sulfinpyrazone): very rarely used in combination with allopurinol or febuxostat in patients in whom hyperuricemia is not controlled with the latter
  - low-dose NSAID/colchicine should be started with urate-lowering therapy for 3-6 mo to avoid an acute flare
  - in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor Cr
- indications for treatment with antihyperuricemic medications include
  - attacks (≥2/yr), tophi, bone erosions/arthritis

Pseudogout (Calcium Pyrophosphate Dihydrate Disease)

Definition
- joint inflammation caused by calcium pyrophosphate (CCP) crystal deposition in connective tissue

Etiology and Pathophysiology
- acute inflammatory arthritis due to phagocytosis of IgG-coated CPPD crystals by neutrophils and subsequent release of inflammatory mediators within joint space
- usually monoarticular
- slower onset in comparison to gout, lasts up to 2-3 wk but is self-limited

Risk Factors
- old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), hemochromatosis

Clinical Presentation
- affects knees, wrists, MCPs, hips, shoulders; less likely elbows, ankles, big toe, spine
- asymptomatic crystal deposition (seen on radiograph only)
- acute crystal arthritis (self-limited flares of acute inflammatory arthritis resembling gout)
- pseudo-OA (progressive joint degeneration, sometimes with episodes of acute inflammatory arthritis)
- pseudo-RA (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- frequently triggered by dehydration, acute illness, surgery, trauma

Investigations
- must aspirate joint to rule out septic arthritis and gout
- CPPD crystals: present in 60% of patients, often only a few crystals, positive birefringence (blue) and rhomboid shaped
- x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

Treatment
- acute CPP: joint aspiration, IA steroid injection, NSAIDs, cool packs, rest, and splinting
- chronic CPP: NSAIDs with gastroprotection and/or low-dose prophylactic colchicine 0.6-1.2 mg/d PO (controversial)

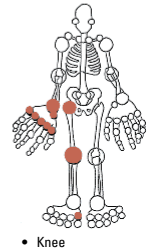

Figure 14. Common sites of involvement of CPPD

EULAR Recommendations for the Management of CPPD
Ann Rheum Dis 2011;70:571-5
1. Pharmacological and non-pharmacological treatment should both be used to manage CPPD.
2. Treating acute CPP crystal arthritis with ice or cool packs, rest, joint aspiration, and IA injection of long-acting glucocorticoids (GCS) may be sufficient for many patients.
3. Acute CPP crystal arthritis can be treated systemically with NSAIDs and low-dose oral colchicine, although their use may be limited in older patients by toxicity and comorbidity.
4. A brief tapering course of oral or parenteral GCS or ACTH may be effective for acute CPP crystal arthritis that is not amenable to IA GCS injection.
5. Low-dose oral colchicine or NSAID can be used as prophylaxis against frequent recurrent acute CPP crystal arthritis.
6. For patients with OA and CPPD, management goals and options are the same as those for OA alone.
7. The order of pharmacological preference for chronic CPP crystal inflammatory arthritis is NSAID and/or colchicine, low-dose corticosteroid, MTX, and hydroxychloroquine.
8. Associated conditions should be treated if detected.
9. There are no disease-modifying treatments for CPP crystal arthritis and no treatment is indicated for asymptomatic chondrocalcinosis.

Non-Articular Rheumatism

Definition
- disorders that primarily affect soft tissues or periarticular structures
- includes bursitis, tendinitis, tenosynovitis, fibromyalgia, and PMR

Polymyalgia Rheumatica

Definition
- characterized by pain and stiffness of the proximal extremities (girdle area)
- common association to GCA
- no muscle weakness

Table 31. PMR Classification Criteria Scoring Algorithm*
Required criteria: age >50 yr, bilateral shoulder aching, and abnormal ESR/CRP

	Points without U/S (0-6)	Points with Abnormal U/S** (0-8)
Morning stiffness duration >45 min	2	2
Hip pain or limited ROM	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis on U/S	N/A	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis on U/S	N/A	1

*A score of 4 or more is categorized as PMR in the algorithm without U/S and a score of 5 or more is categorized as PMR in the algorithm with U/S
**Optional U/S criteria
Ann Rheum Dis 2012;71:484-492

Epidemiology
- incidence: 50 in 100,000 per yr in those >50 yr
- age of onset typically >50 yr, F:M=2:1

Clinical Presentation
- constitutional symptoms prominent (fever, weight loss, malaise)
- pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs)
- prolonged morning stiffness
- physical exam reveals tender muscles, but no true weakness or atrophy

Investigations
- blood work: often shows anemia of chronic disease, elevated platelets, elevated ESR and CRP, and normal CK; up to 5% of PMR reported with normal inflammatory markers

Treatment
- goal of therapy: symptom relief
- start with prednisone 12.5-25 mg PO once daily, reconsider diagnosis if no response within several days
- taper slowly with improvement over 1 yr period with close monitoring, if in remission taper until discontinued
- relapses should be diagnosed and treated on clinical basis; do not treat a rise in ESR as a relapse
- treat relapses aggressively (50% relapse rate)
- monitor for steroid side effects, glucocorticoid-induced osteoporosis prevention, and follow for symptoms of GCA (H/A, jaw claudication, scalp tenderness)

Fibromyalgia

Definition
- chronic (>3 mo), widespread (axial, left- and right-sided, upper and lower segment), non-articular pain with characteristic tender points

Diagnosis

Table 32. 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia

Criteria	Comments
Widespread Pain Index = number of areas in which the patient had pain over the last wk (max score = 19): L and R: shoulder girdle, upper arm, lower arm, hip, upper leg, lower leg, jaw One Area: chest, abdomen, upper back, lower back, neck Symptom Severity (SS) Score = sum of: a) severity of fatigue b) waking unrefreshed c) cognitive symptoms over the past wk d) extent of somatic symptoms (IBS, H/A, abdominal pain/cramps, dry mouth, fever, hives, ringing in ears, vomiting, heartburn, dry eyes, SOB, loss of appetite, rash, hair loss, easy bruising, etc.) All (a-d) rated on 0-3 scale: 0 = no problem, 1 = mild, 2 = moderate, 3 = severe	A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met: 1. Widespread Pain Index (WPI) ≥7 and SS score ≥5 or WPI 3-6 and SS score ≥9 2. Symptoms have been present at a similar level for at least 3 mo 3. The patient does not have a disorder that would otherwise explain the pain

Arthrit Care and Res 2010;62(5):600-610

Epidemiology

- F:M=3:1
- primarily ages 25-45, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness

Clinical Presentation

- widespread aching, stiffness
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent wakening
- symptoms aggravated by physical activity, poor sleep, emotional stress
- neurologic symptoms of hyperalgesia, paresthesias, allodynia
- associated with irritable bowel or bladder syndrome, migraines, tension H/As, restless leg syndrome, obesity, depression, and anxiety
- physical exam should reveal only tenderness with palpation of soft tissues, with no specificity for trigger/tender points

Investigations

- blood work: includes TSH; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a CTD or inflammatory arthritis
- laboratory sleep assessment

Treatment

- non-pharmacological therapy
  - counseling on self-management strategies
  - graded exercise programs including aerobic (>20 min/d, 2-3 d/wk) and resistance training (>8 repetitions per exercise, 2-3 d/wk)
  - other therapies with some evidence: acupuncture, CBT, hydrotherapy, meditative movement (yoga, Tai chi)
- pharmacological therapy (to help with symptoms, not curative)
  - low-dose tricyclic antidepressant (e.g. amitriptyline)
    - for sleep restoration
    - select those with lower anticholinergic side effects
  - SNRI: duloxetine, milnacipran
  - anticonvulsant: pregabalin, gabapentin
  - for analgesic treatment, opioids are not encouraged. NSAIDs are no longer encouraged (controversial)

Prognosis

- variable; usually chronic, waxes and wanes, with some pain and fatigue that usually persists

Table 33. Clinical Features of Inflammatory Myopathy vs. Polymyalgia Rheumatica vs. Fibromyalgia

	Polymyositis	PMR	Fibromyalgia
Epidemiology	F>M, 40-50 yr	F>M, >50 yr	F>M, 25-45 yr
Muscle Involvement	Proximal muscle	Proximal muscle	Diffuse
Weakness	Yes	No	No
Pain	Painless	Painful	Painful
Stiffness	Present	Significant morning and gelling stiffness (shoulders, neck, hips)	May have morning stiffness
Investigations	Muscle biopsy, CK, EMG, rule out malignancy	ESR/CRP, rule out GCA	Sleep assessment, TSH
ESR/CRP	Usually normal	Markedly elevated	Normal
Treatment	High-dose steroids, immunosuppressants	Low-dose steroids	Exercise, sleep restoration

Common Medications

Table 34. Common Medications for Osteoarthritis

Class	Generic Drug Name	Trade Name	Dosing (PO)	Indications	Contraindications	Adverse Effects
Analgesics	acetaminophen	Tylenol®	1000 mg TID q4 h (3 g daily max)	1st line	Severe liver disease/ impairment	Hepatotoxicity, overdose, potentiates warfarin
NSAIDs	ibuprofen diclofenac diclofenac/ misoprostol naproxen meloxicam	Advil® Voltaren® Arthrotec® Naprosyn® Aleve® Mobicox®	200-600 mg TID 25-50 mg TID 50-75/200 mg TID 125-500 mg BID 7.5-15 mg once daily	2nd line	GI bleed, renal impairment, allergy to ASA, NSAIDs, pregnancy (T3), anticoagulants	Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome
COX-2 Inhibitors	celecoxib	Celebrex®	200 mg once daily	Dyspepsia/GERD	Renal impairment, cardiovascular disease, GI Bleed	Same as NSAIDs above

Other Treatments	Comments
Combination analgesics (acetaminophen + codeine, acetaminophen + NSAIDs)	Enhanced short-term effect compared to acetaminophen alone, can limit dosage of each to minimize adverse effects increased range of adverse effects: sedation, constipation, nausea, GI upset
IA corticosteroid injection	Short-term (wk-mo), joint specific treatment manages IA inflammatory process when infection has been ruled out Theoretical risk of cartilage damage and tendon weakening if used more frequently than q3 mo
Topical NSAIDs	Topical diclofenac (Pennsaid®, Voltaren Emulgel®) May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy, better on small joints
Capsaicin cream	Mild decrease in pain
Glucosamine sulfate ± chondroitin	Limited evidence of benefit in OA knee. No regulation by Health Canada

Table 35. DMARDs

Generic Drug Name	Trade Name	Dosing	Contraindications	Adverse Effects
COMMONLY USED				
hydroxychloroquine $	Plaquenil®	400 mg PO once daily initially 200-400 mg PO once daily maintenance (5 mg/kg ideal body weight per day to a maximum of 400 mg/d)	Retinal disease	GI symptoms, skin rash, macular damage, neuromyopathy Requires annual ophthalmological screening to monitor for retinopathy
sulfasalazine $	Salazopyrim® Azulfidine® (US)	1000 mg PO BID-TID	Sulfa/ASA allergy	GI symptoms, rash, H/A, leukopenia
methotrexate $	Rheumatrex® Folex/Mexate®	7.5-25 mg PO/SC weekly	Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EtOH use, moderate to severe kidney disease	Oral ulcers, GI symptoms, cirrhosis, myelosuppression, pneumonitis, tubular necrosis, fatigue
azathioprine $	Imuran®	2 mg/kg/d PO once daily	Kidney/liver disease thiopurine S-methyltransferase (TPMT) deficiency	Rash, pancytopenia (especially decrease WBC, increase AST and ALT), biliary stasis, vomiting, diarrhea
Mycophenolate Mofetil/ Sodium $$	Cellcept® Myfortic®	500-1500 mg PO BID	Pregnancy or breastfeeding, severe immunodeficiency	GI symptoms, cytopenias, headaches, skin rashes
leflunomide $$	Arava®	10-20 mg PO once daily	Liver disease, lung disease, pregnancy	Alopecia, GI symptoms, liver dysfunction, interstitial pulmonary fibrosis, HTN
NOT COMMONLY USED				
cyclosporine $$	Neoral®	2.5-3 mg/kg/d divided and given in 2 doses PO	Kidney/liver disease, infection, HTN	HTN, decreased renal function, hair growth, tremors, bleeding
gold (injectable) $	Solganal® Myochrysine®	50 mg IM weekly after gradual introduction	IBD, kidney/liver disease	Rash, mouth soreness/ulcers, proteinuria, marrow suppression
cyclophosphamide $	Cytoxan®	1 g/m^2/mo IV as per protocol	Kidney/liver disease, neutropenia	Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility, bladder cancer

Table 35. DMARDs

Generic Drug Name	Trade Name	Dosing	Contraindications	Adverse Effects	Mechanism
NEWER DMARDs (Biologics)					
etanercept $$$	Enbrel®	25 mg biweekly or 50 mg weekly SC	Fusion protein of TNF receptor and Fc portion of IgG		
infliximab $$$	Remicade®	3-5 mg/kg IV q8 wk	Chimeric mouse/human monoclonal anti-TNF		
adalimumab $$$	Humira®	40 mg SC q2 wk	Monoclonal anti-TNF		
golimumab $$$	Simponi®	50 mg SC q1 mo or 2 mg/kg q8 wk	Monoclonal anti-TNF		
certolizumab $$$	Cimzia®	400 mg SC q2 wk x3 then 200 mg SC q4 wk	PEGylated monoclonal anti-TNF		
apremilast $$$	Otezla®	Day 1: 10 mg (AM) PO, titrate up to 30 mg BID by day 6	PDE4 inhibitor which reduces production of TNF-α		
abatacept $$$	Orencia®	500-1000 mg IV infusion q1 mo or 125 mg SC q1 wk	Costimulation modulator of T cell activation		
rituximab $$$	Rituxan®	1 g x2 IV infusions, 2 wk apart q6 mo	Causes B cell depletion, binds to CD20		
tocilizumab $$$	Actemra®	4-8 mg/kg IV q4 wk or 162 mg SC q1-2 wk	IL-6 receptor antagonist		
tofacitinib $$	Xeljanz®	5 mg BID	Selective JAK 1/3 inhibitor and thus interferes with JAK-STAT signaling pathway		
upadacitinib $$	Rinvoq®	15 mg once daily	Selective JAK1 inhibitor and thus interferes with JAK-STAT signaling pathway		
secukinumab $$$	Cosentyx®	150 mg monthly	Blocks IL-17A		

*Of note, biosimilars are increasingly becoming available for select biologics."Biosimilars" are drugs nearly identical to previously approved biologics which are allowed to enter markets following the expiry of patents belonging to the original biologic. Biosimilars are currently available for adalimumab, etanercept and rituximab in Canada

Landmark Rheumatology Trials

Trial Name	Reference	Clinical Trial Details
RHEUMATOID ARTHRITIS		
COMET	Lancet 2008;372:375-82	**Title**: Comparison of Methotrexate Monotherapy with a Combination of Methotrexate and Etanercept in Active, Early, Moderate to Severe Rheumatoid Arthritis (COMET): A Randomised, Double-Blind, Parallel Treatment Trial **Purpose**: To compare the efficacy of MTX monotherapy or MTX plus etanercept for remission and radiographic non-progression in RA patients. **Methods**: 542 RA MTX-naive outpatients with moderate-to-severe disease for 3-24 mo were randomly assigned to MTX alone (titrated from 7.5-20 mg/wk) or MTX (same titration) plus etanercept 50 mg/wk. **Results**: Clinical remission was achieved in 50% of patients on combined treatment vs. 28% taking MTX alone (difference, 22.05%; P<0.0001). 80% and 59%, respectively, achieved radiographic non-progression (difference, 20.98%; P<0.0001). Both groups experienced similar adverse events. **Discussion:** 1 yr of treatment with etanercept plus MTX can achieve clinical remission and radiographic non-progression in early severe RA.
ERA	NEJM 2000;343:1586-93	**Title**: A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis **Purpose**: To investigate the efficacy of etanercept in reducing disease activity and joint damage in patients with early and active RA. **Methods**: 632 patients received either SC etanercept (10 or 25 mg/wk) twice weekly or oral MTX (19 mg/wk) for 12 mo. Clinical response was defined by criteria of the American College of Rheumatology. **Results**: Patients on 25 mg etanercept improved quicker than those on MTX, with significantly more improvements in disease activity within 6 mo (P<0.05). During the first 6 and 12 mo, there were significantly greater increases in mean erosion scores in the MTX group (P=0.007). Fewer adverse events (P=0.02) and infections (P=0.006) were seen in 25 mg etanercept. **Conclusion**: In patients with early active RA, etanercept more rapidly reduced symptoms and slowed joint damage as compared to MTX.
BeSt	Arthritis Rheum 2005;52:3381-90	**Title**: Clinical and Radiographic Outcomes of Four Different Treatment Strategies in Patients with Early Rheumatoid Arthritis (the BeSt Study): A Randomized, Controlled Trial **Purpose**: To identify the optimal therapeutic strategy for preventing long-term joint damage and functional decline in RA. **Methods**: 508 patients were randomly assigned to 1 of 4 therapeutic strategies: (1) sequential disease-modifying antirheumatic drug monotherapy, (2) step-up combination therapy, (3) initial combination therapy with tapered high-dose prednisone, or (4) initial combination therapy with infliximab. **Results**: At 3 mo, groups 3 and 4 showed significantly greater functional improvement (as defined by the Dutch version of the Health Assessment Questionnaire (D-HAQ)) with mean scores of 0.6, as compared to mean scores of 1.0 in groups 1 and 2 (P<0.001). At 1 yr, mean D-HAQ scores in groups 3 and 4 were 0.5, as compared to 0.7 in groups 1 and 2 (P=0.009). **Conclusion**: As compared to sequential monotherapy or step-up combination therapy, initial combination therapy with prednisone or infliximab led to earlier functional improvements and less radiographic damage in patients with early RA.
Infliximab and MTX	NEJM 2000;343:1594-602	**Title**: Infliximab and Methotrexate in the Treatment of Rheumatoid Arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group **Purpose**: To assess infliximab for potential sustained benefits and effects on joint damage in RA. **Methods**: 428 patients who had active RA despite MTX therapy were treated with IV infliximab (3 or 10 mg/kg every 4 or 8 wk plus oral MTX for 54 wk) or placebo. **Results**: As compared to MTX alone, infliximab plus MTX significantly reduced signs and symptoms of RA (clinical response, 51.8% vs. 17.0%; P<0.001). There was greater evidence of joint damage on MTX alone but not on infliximab plus MTX (mean change in radiographic score, 7.0 vs. 0.6, P<0.001). **Conclusion**: Repeated doses of infliximab plus MTX in persistently active RA was clinically effective and slowed the progression of joint damage.

Trial Name	Reference	Clinical Trial Details
Treatment of Active Rheumatoid Arthritis with Leflunomide Compared with Placebo and Methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Strand et al. 1999	Arch Intern Med 1999;159:2542-50	**Title**: Treatment of Active Rheumatoid Arthritis with Leflunomide Compared with Placebo and Methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group **Purpose**: To compare the safety and efficacy of leflunomide vs. MTX in patients with active RA. **Methods**: 482 patients with active RA were randomly assigned to receive leflunomide (20 mg/d), MTX (7.5-15 mg/wk), or placebo. **Results**: Clinical response and success rates on leflunomide (52% and 41%) and MTX (46% and 35%) were significantly greater than those on placebo (26% and 19%) (P<0.001). On leflunomide, common adverse events included gastrointestinal complaints, skin rash, and reversible alopecia. **Conclusion**: In patients with active RA, leflunomide was associated with better clinical responses than placebo and had similar efficacies as MTX.
PREMIER	Arthritis Rheum 2006;54:26-37	**Title**: The PREMIER Study: a Multicenter, Randomized, Double-Blind Clinical Trial of Combination Therapy with Adalimumab plus Methotrexate versus Methotrexate Alone or Adalimumab Alone in Patients with Early, Aggressive Rheumatoid Arthritis Who Had Not Had Previous Methotrexate Treatment **Purpose**: To compare the efficacy and safety of adalimumab plus MTX versus MTX alone or adalimumab alone in patients with early, aggressive RA who were MTX-naive. **Methods**: 799 patients with active disease <3 yr were randomly assigned to adalimumab 40 mg SC every other wk plus oral MTX, adalimumab 40 mg SC every other wk, or oral MTX weekly. **Results**: American College of Rheumatology 50% improvement was achieved in significantly more patients on combination therapy (62%) than MTX or adalimumab (46% and 41%, respectively; both P<0.001). Patients on combination therapy had significantly less radiographic progression (P<0.002) than those on either monotherapy. 49% of patients on combination therapy achieved remission at 2 yr. **Conclusion**: Adalimumab plus MTX was significantly superior to either MTX or adalimumab alone in early, aggressive RA.
OSTEOARTHRITIS		
Hyaluronan	Ann Rheum Dis 2010;69:1097-1102	**Title**: Intra-Articular Hyaluronan is without Clinical Effect in Knee Osteoarthritis: a Multicentre, Randomised, Placebo-Controlled, Double-Blind Study of 337 Patients Followed for 1 Year **Purpose**: To assess the long-term safety and efficacy of 5 hyaluronan IA injections in knee osteoarthritis. **Methods**: 337 patients with knee osteoarthritis and a Lequesne algofunctional index score (LFI) ≥10 received IA hyaluronan product (sodium hyaluronate; Hyalgan®) or saline weekly for 5 wk. **Results**: Treatment had no significant effect on time to recurrence or baseline change in LFI or walking pain. There were also no significant differences in paracetamol consumption, patients' global assessment, responder rates, or adverse events. **Conclusion**: Hyaluronan injections were not clinically effective in patients with osteoarthritis of the knee with moderate-severe disease (LFI≥10).
SYSTEMIC LUPUS ERYTHEMATOSUS		
Belimumab	Lancet 2011;377:721-31	**Title**: Efficacy and Safety of Belimumab in Patients with Active Systemic Lupus Erythematosus: a Randomised, Placebo-Controlled, Phase 3 Trial **Purpose**: To assess the efficacy and safety of belimumab in patients with active SLE. **Methods**: 867 patients (aged ≥18 yr) who were seropositive with scores of ≥6 on SELENA-SLEDAI were randomly assigned to belimumab 1 mg/kg or 10 mg/kg, or placebo plus standard of care (based on disease manifestation and local guidelines). **Results**: Significantly higher SRI (SLE Responder Index) rates occurred with belimumab 1 mg/kg (51%, OR 1.55; P=0.0129) and 10 mg/kg (58%, 1.83; P=0.0006) than placebo (44%). There was a greater frequency of SELENA-SLEDAI reduction by ≥4 points with belimumab 1 mg/kg (53%, 1.51; P=0.0189) and 10 mg/kg (58%, 1.71; P=0.0024) than placebo (46%). **Conclusion**: Belimumab may be the first targeted biologic that is specifically approved for SLE.
Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis. Ginzler et al. 2005	NEJM 2005;353:2219-28	**Title**: Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis **Purpose**: To investigate if mycophenolate mofetil is effective for treating lupus nephritis. **Methods**: 140 patients with active lupus nephritis were randomly assigned to oral mycophenolate mofetil (1000 mg/d increased to 3000 mg/d) or monthly IV cyclophosphamide (0.5 g/m2 increased to 1.0 g/m^2). **Results**: 22.5% of patients on mycophenolate mofetil and 5.8% of those on cyclophosphamide experienced complete remission (absolute difference, 16.7%; 95% CI, 5.6-27.9%; P=0.005), thus demonstrating that mycophenolate mofetil is more efficacious than cyclophosphamide. **Conclusion**: In active lupus nephritis, mycophenolate mofetil was more effective than IV cyclophosphamide in inducing remission and had a better safety profile.
CONNECTIVE TISSUE DISORDERS		
Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis. Pagnoux et al. 2008	NEJM 2008;359:2790-803	**Title**: Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis **Purpose**: To compare azathioprine (AZA) and MTX for safety and efficacy in Wegener's granulomatosis and microscopic polyangiitis. **Methods**: 159 patients who achieved remission with IV cyclophosphamide and corticosteroids were randomly assigned to receive oral AZA or MTX for 12 mo. **Results**: The rates of adverse events (requiring discontinuation of the study drug or causing death) were not significantly different between groups. Event-free survival was also not significantly different between groups. **Conclusion**: In patients with Wegener's granulomatosis and microscopic polyangiitis, AZA and MTX are similar alternatives for maintenance therapy after initial remission.
CYCLOPS	Ann Intern Med 2009;150:670-80	**Title**: Pulse versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: a Randomized Trial **Purpose**: To compare the efficacy of pulse cyclophosphamide vs. daily oral cyclophosphamide for inducing remission in ANCA-associated vasculitis. **Methods**: 149 patients with newly diagnosed generalized ANCA-associated vasculitis with renal involvement received cyclophosphamide 15 mg/kg every 2-3 wk (pulse), or daily cyclophosphamide 2 mg/kg orally, plus prednisolone. **Results**: There was no significant difference in time to remission (P=0.59) or percentage of patients who went into remission at 9 mo (88.1% in pulse vs. 87.7% in oral). The oral group had higher cumulative cyclophosphamide doses (P<0.001). Lower rates of leukopenia were seen in the pulse group (hazard ratio, 0.41; 95% CI, 0.23 to 0.71). **Conclusion**: In ANCA-associated vasculitis, pulse cyclophosphamide induced remission as effectively as the daily oral regimen, required less cumulative cyclophosphamide, and caused fewer cases of leukopenia.
Cyclophosphamide vs. Placebo in Scleroderma Lung Disease. Tashkin et al. 2006	NEJM 2006;354:2655-66	**Title**: Cyclophosphamide versus Placebo in Scleroderma Lung Disease **Purpose**:To determine the efficacy of oral cyclophosphamide in patients with active alveolitis and scleroderma-related ILD. **Methods**: 158 patients with scleroderma, restrictive lung physiology, dyspnea, and evidence of inflammatory ILD received oral cyclophosphamide (≤2 mg/kg/d) or placebo for 1 yr. **Results**: The mean absolute difference in 12-mo adjusted FVC between cyclophosphamide and placebo was 2.53% (95% CI, 0.28 to 4.79%), indicating great efficacy of cyclophosphamide (P<0.03). The difference in FVC between groups was sustained at 24 mo. **Conclusion**: In patients with symptomatic scleroderma-related ILD, oral cyclophosphamide had significant clinical benefit.

Trial Name	Reference	Clinical Trial Details
WGET	NEJM 2005;352:351-361	**Title**: Etanercept plus Standard Therapy for Wegener's Granulomatosis **Purpose**: To investigate the safety and efficacy of etanercept for remission maintenance in GPA. **Methods**: 180 patients with GPA were randomly assigned to receive either etanercept or placebo, in addition to standard treatment (glucocorticoids plus cyclophosphamide or MTX). **Results**: No significant differences were observed between the etanercept and control groups in the rates of stable periods of low-level disease activity (86.5% vs. 90.6%, P=0.32), sustained remission (69.7% vs. 75.3%, P=0.39), or the time necessary to reach those outcomes. Disease flares and adverse events were common in both groups but not significantly different. **Conclusion**: Etanercept is not effective for remission maintenance in GPA.
IMPROVE	JAMA 2010;304:2381-88	**Title**: Mycophenolate Mofetil versus Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis (AAV): a Randomized Controlled Trial **Purpose**: To compare the efficacy of mycophenolate mofetil vs. azathioprine (AZA) preventing relapses in patients with AAV. **Methods**: Following remission induction with cyclophosphamide and prednisolone,156 patients with newly diagnosed AAV were randomly assigned to AZA (initiated at 2 mg/kg/d) or mycophenolate mofetil (initiated at 2000 mg/d). **Results**: The mycophenolate mofetil group experienced significantly more relapses (55%) as compared to AZA (37.5%) (hazard ratio for mycophenolate mofetil, 1.69, 95% CI, 1.06-2.70; P=0.03). There was no significant difference in the rates of severe adverse events between groups. **Conclusion**: Mycophenolate mofetil was less effective than AZA for maintaining disease remission in AAV.
RAVE	NEJM 2010;363:221-32	**Title**: Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis **Purpose**: To investigate if rituximab is more effective and/or safer than a cyclophosphamide for treating AAV. **Methods**: 197 ANCA-positive patients randomly assigned to receive rituximab (375 mg/m^2 for 4 wk) or cyclophosphamide (2 mg/kg/d). **Results**: 64% of the rituximab group reached the primary endpoint (remission of disease without the use of prednisone at 6 mo), as compared with 53% of controls (noninferiority, P<0.001). Rituximab was more effective than cyclophosphamide for inducing remission of relapsing disease; 67% vs. 42% reached the primary endpoint (P=0.01). **Conclusion**: In severe AAV, rituximab was noninferior to cyclophosphamide for remission induction and may be superior in relapsing disease.
MAINRITSAN3	Ann Intern Med 2020;173:179-187	**Title**: Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Trial **Purpose**: To assess the efficacy of prolonged rituximab therapy in reducing AAV relapses in patients in complete remission following an initial phase of maintenance therapy. **Methods**: 68 patients were randomized to receive an infusion of rituximab or placebo every 6 mo for 18 mo. **Results**: At 28 mo, estimates of relapse-free survival were 96% and 74% in the rituximab and placebo groups, respectively, representing an absolute difference of 22% (CI, 9-36%) and a hazard ratio of 7.5 (CI, 1.67-33.7) (P=0.008). **Conclusion**: Prolonged rituximab therapy resulted in lower rates of AAV relapse than standard maintenance therapy.
GOUT		
Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout. Becker et al. 2005	NEJM 2005;353:2450-61	**Title**: Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout **Purpose**: To investigate the use of febuxostat as a potential alternative to allopurinol for patients with hyperuricemia and gout. **Methods**: 762 patients with gout and with serum urate ≥8.0 mg/dL were randomly assigned to receive either daily febuxostat (80 or 120 mg) or daily allopurinol (300 mg) for 52 wk. **Results**: Primary endpoint (serum urate <6.0 mg/dL at the last 3 monthly measurements) occurred in 53% of patients on febuxostat 80 mg, 62% on febuxostat 120 mg, and 21% on allopurinol (P<0.001 for both febuxostat groups vs. allopurinol). The overall incidence of gout flares during wk 9-52 was similar in all groups and decreased with continued treatment. **Conclusion**: In patients with hyperuricemia and gout, febuxostat was more effective than allopurinol at lowering serum urate.
ANKYLOSING SPONDYLITIS		
ATLAS	Arthritis Rheum 2006;54:2136-46	**Title**: Efficacy and Safety of Adalimumab in Patients with Ankylosing Spondylitis: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial **Purpose**: To assess the safety and efficacy of adalimumab in patients with active AS. **Methods**: 208 AS patients were randomly assigned to SC injection of adalimumab (40 mg every other wk) or placebo for 24 wk. Primary outcome was a 20% response according to the Assessment in AS International Working Group (ASA20). **Results**: 58.2% of adalimumab-treated patients reached an ASAS20 response at wk 12 vs. 20.6% of placebo-treated patients (P<0.001). Adalimumab also demonstrated significantly greater ASAS40 and ASAS5/6 responses at wk 12 and 24 (P<0.001). Significantly more adverse events were seen with adalimumab. **Conclusion**: Adalimumab was well-tolerated and clinically effective in treating active AS.
ASSERT	Arthritis Rheum 2005;52:582-91	**Title**: Efficacy and Safety of Infliximab in Patients with Ankylosing Spondylitis: Results of a Randomized, Placebo-Controlled Trial (ASSERT) **Purpose**: To evaluate the efficacy and safety of infliximab in AS. **Methods**: 279 patients were randomly assigned to receive 5 mg/kg infliximab infusions at wk 0, 2, 6, 12, and 18, or placebo. Primary outcome was a 20% response according to the Assessment in AS International Working Group (ASA20). **Results**: As compared with placebo, significantly more patients on infliximab achieved the primary outcome (61.2% vs. 19.2%) (P<0.001). Infliximab produced clinical benefits beginning at wk 2 that were sustained over the 24 wk. Adverse events were common in both groups but generally mild-moderate in severity. **Conclusion**: In patients with AS, infliximab was clinically effective and well tolerated over 24 wk.
SPINE	Ann Rheum Dis 2011;70:799-804	**Title**: Efficacy of Etanercept on Rheumatic Signs and Pulmonary Function Tests in Advanced Ankylosing Spondylitis: Results of a Randomized Double-Blind Placebo-Controlled Study (SPINE) **Purpose**: To assess the efficacy of etanercept (ETN) in advanced AS. **Methods**: 82 patients with severe, active AS that were refractory to NSAIDs and anti-TNF naive were treated with ETN 50 mg once per wk or placebo. **Results**: Over 12 wk, there were significantly greater improvements in the Bath AS Disease Activity Index (BASDAI) in the ETN group vs. placebo group (-19.8±16.5 vs. -11.0±16.4, P=0.019). ETN also improved CRP levels (P<0.001), total back pain (P=0.010), and FVC (P=0.006). **Conclusion**: In advanced AS, ETN has short-term efficacy for improving pain, CRP, spinal mobility and pulmonary function.
Sulfasalazine	Arthritis Rheum 1995;38:618-27	**Title**: Sulfasalazine in the Treatment of Spondylarthropathy. A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study **Purpose**: To evaluate the safety and efficacy of SSZ in treating spondylarthropathy. **Methods**: 351 patients with active disease despite treatment with NSAIDs received SSZ (3 g/d) or placebo. Primary efficacy outcomes included the patient's and physician's overall assessments, pain, and morning stiffness. **Results**: 60% of patients taking SSZ improved by at least 1/5 points on patient assessment of disease activity, in contrast to 44% taking placebo (only significant difference among 4 primary outcomes). SSZ had greater clinical efficacy in a subgroup of patients with psoriatic arthritis, as measured by primary efficacy variables and joint inflammation. **Conclusion**: SSZ was more effective than placebo in treating active spondylarthropathy, particularly in patients with psoriatic arthritis.

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U Urology

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Acronyms

ADT	androgen deprivation therapy
AFP	alpha-fetoprotein
ART	assisted reproductive technologies
ASA	acetylsalicylic acid
AUA	American Urological Association
BBD	bladder and bowel dysfunction
BCG	Bacillus Calmeâtte-Guérin
BPH	benign prostatic hyperplasia
BPKVP	bipolar plasma kinetic vaporization of the prostate
CAH	congenital adrenal hyperplasia
CaP	cancer of the prostate
CBI	continuous bladder irrigation
CF	cystic fibrosis
CFU	colony-forming unit
CHF	congestive heart failure
CIC	clean intermittent catheterization
CIS	carcinoma in situ
CMG	cystometrogram
CRPC	castrate-resistant prostate cancer
CTU	CT urography
CUA	Canadian Urological Association
CVA	costovertebral angle
d/c	discharge
DHT	dihydrotestosterone
DMSA	dimercaptosuccinic acid
DRE	digital rectal exam
DSD	detrusor sphincter dyssynergia
EBRT	external beam radiation therapy
ED	erectile dysfunction
EPS	expressed prostatic secretions
FNA	fine needle aspiration
GA	general anesthesia
GAG	glycosaminoglycan
HIFU	high-intensity focused ultrasound
HPF	high power field
HPTA	hypothalamic-pituitary-testicular axis
HRR	homologous recombination repair
ICSI	intracytoplasmic sperm injection
IFN-α	interferon-alpha
IL-2	interleukin-2
IPSS	International Prostate Symptom Score
ISD	intrinsic sphincter deficiency
IUI	intrauterine insemination
IVF	in vitro fertilization
IVP	intravenous pyelogram
KUB	kidneys, ureters, bladder
LFT	liver function test
LMN	lower motor neuron
LUTS	lower urinary tract symptoms
MET	medical expulsive therapy
MS	multiple sclerosis
MVC	motor vehicle collisions
NMIBC	non-muscle invasive bladder cancer
NSGCT	non-seminomatous germ cell tumour
OAB	overactive bladder
OPQRST	onset, position, quality, radiation, severity, temporality, déjà vu
PCa	prostate cancer
PCKD	polycystic kidney disease
PCNL	percutaneous nephrolithotomy
PDE	phosphodiesterase
PFMT	pelvic muscle floor training
PGE1	prostaglandin E1
PID	pelvic inflammatory disease
PLND	pelvic lymph node dissection
PMC	pontine micturition centre
POD	post-obstructive diuresis
PSA	prostate specific antigen
PUV	posterior urethral valve
PVD	peripheral vascular disease
PVP	photoselective vaporization of the prostate (GreenLight™Laser)
PVR	post-void residual
QOL	quality of life
RCC	renal cell carcinoma
RCT	randomized controlled trial
RFA	radio-frequency ablation
RP	radical prostatectomy
RPLND	retroperitoneal lymph node dissection
RR	respiratory rate
RTA	renal tubular acidosis
RUG	retrograde urethrogram
SA	semen analysis
SCC	squamous cell carcinoma
SEEK PP	*Staphylococcus saprophyticus, E. coli, Enterococcus, Klebsiella, Proteus, Pseudomonas*
SFU	Society of Fetal Urology
SLN	sentinel lymph node
SUI	stress urinary incontinence
SWL	(extracorporeal) shockwave lithotripsy
TNM	tumour node metastasis
TMP/SMX	trimethoprim/sulfamethoxazole
TRUS	transrectal ultrasound
TUIP	transurethral incision of the prostate
TUMT	transurethral microwave therapy
TURBT	transurethral resection of bladder tumour
TURP	transurethral resection of the prostate
U/O	urine output
UC	urothelial carcinoma
UMN	upper motor neuron
UPJ	ureteropelvic junction
URS	ureterorenoscopy
UTD	urinary tract dilation
UTI	urinary tract infection
UVJ	ureterovesical junction
VB1	voided bladder, initial (urethra)
VB2	voided bladder, midstream (bladder)
VB3	voided bladder, post-massage/ digital rectal exam
VCUG	voiding cystourethrogram
VIU	visual internal urethrotomy
VUR	vesicoureteral reflux
WHO	World Health Organization

Basic Anatomy Review

- recall that the anatomical position of the penis is erect; therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis

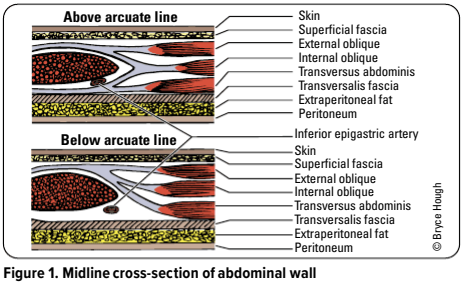

Figure 1. Midline cross-section of abdominal wall

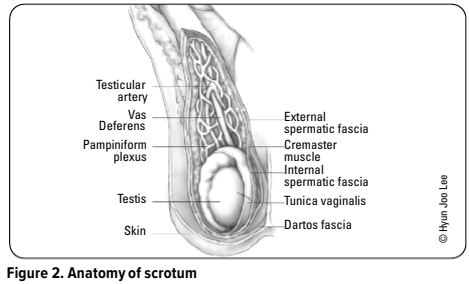

Figure 2. Anatomy of scrotum

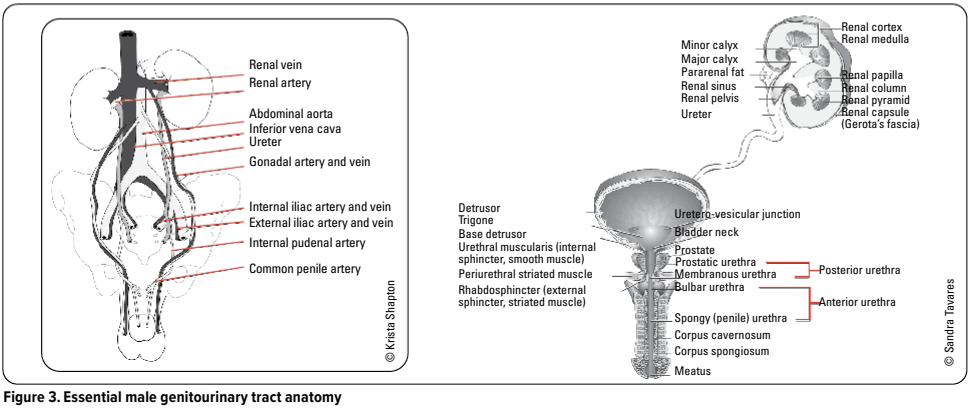

Figure 3. Essential male genitourinary tract anatomy

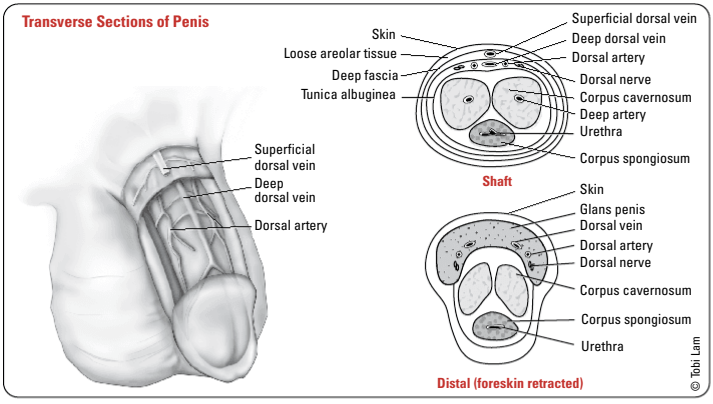

Figure 4. Cross section of the penis

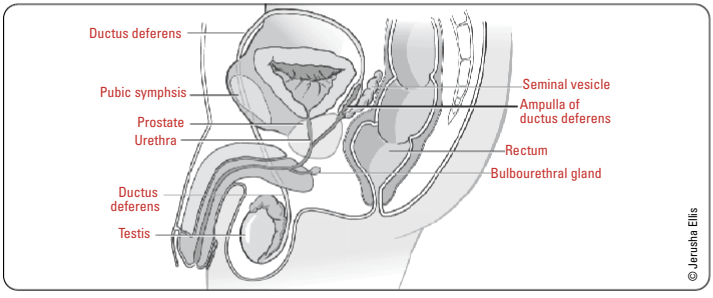

Figure 5. Median sagittal section of the male pelvis and perineum

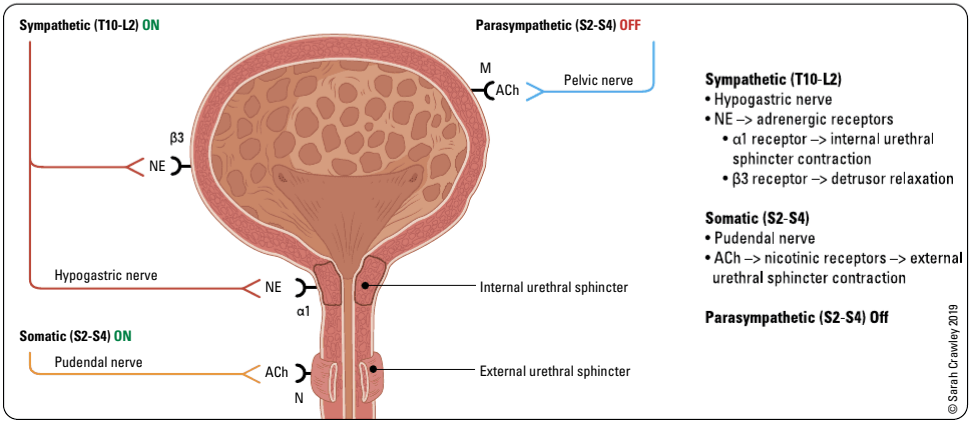

Figure 6. Bladder innervation during storage phase

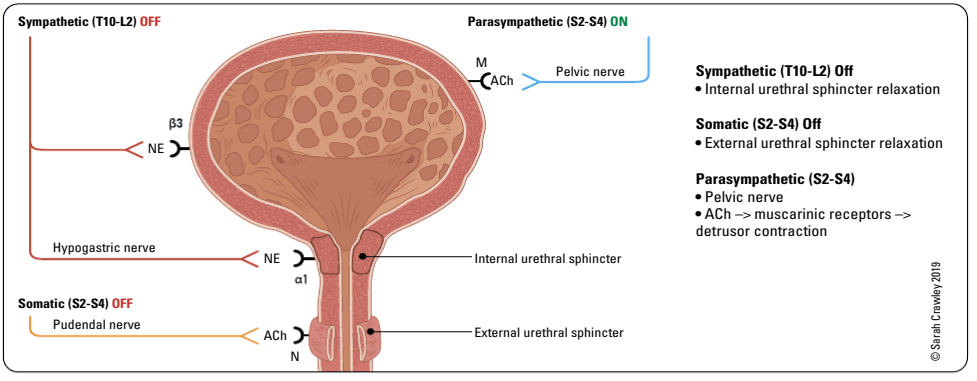

Figure 7. Bladder innervation during voiding phase

Urologic History

- follow OPQRSTU approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
  - assess the behavioural and psychological impact of symptoms on patient quality of life
- urinary habits
  - LUTS (see *Lower Urinary Tract Symptoms, U7*)
  - storage symptoms: frequency, urgency (rush to toilet), nocturia (FUN)
  - voiding symptoms: stream changes/straining, hesitancy, incomplete emptying, post-void dribbling (SHED)
  - dysuria: burning, pain on voiding
  - hematuria: blood clots, red/pink tinged urine (see *Hematuria, U4*)
  - incontinence: stress, urgency, mixed, overflow (see *Urinary Incontinence, U6*)
- sexual function
  - scrotal mass (see *Scrotal Masses, U32*)
  - ED (see *Erectile Dysfunction, U33*)
  - female sexual dysfunction (dyspareunia, low desire, arousal disorder, orgasmic dysfunction)
  - infertility (see *Infertility, U37*)
- associated symptoms
  - N/V
  - bowel dysfunction
- constitutional symptoms
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise, bone pain
- risk factors: past urologic disease (e.g. UTI, stones, STI, cancers, anatomic abnormalities), FMHx, medications, lifestyle factors (e.g. smoking, alcohol, inactivity), trauma, previous surgical procedure

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant vascular disease. If there is new onset ED, consider screening for DM and CAD risk factors

Hematuria

Macroscopic (Gross) Hematuria

Gross, painless hematuria in adults is bladder cancer until proven otherwise

Definition

- blood in the urine that can be seen with the naked eye

Classification

- see Nephrology, NP24

Etiology

Table 1. Etiology by Age Group

Age (yr)	Etiology	
0-20	UTI, glomerulonephritis, congenital abnormalities	
20-40	UTI, stones, bladder tumour, exercise	
40-60	Male: bladder tumour, stones, UTI, prostate cancer	Female: UTI, stones, bladder tumour
>60	Male: BPH, bladder tumour, UTI, RCC, prostate cancer	Female: bladder tumour, UTI, RCC

Table 2. Etiology by Type

Pseudohematuria	Infectious/Inflammatory	Malignancy	Benign	Structural	Hematologic
Vaginal bleeding Dyes (beets, rhodamine B in candy and juices) Hemoglobin (hemolytic anemia) Myoglobin (rhabdomyolysis) Drugs (rifampin, phenazopyridine, phenytoin) Porphyria Laxatives (phenolphthalein)	Pyelonephritis Cystitis Urethritis Glomerulonephritis Interstitial nephritis Tuberculosis	RCC (mainly adults) Urothelial cancer Wilms' tumour (mainly pediatric) Prostate cancer Leukemia	BPH Polyps Exercise-induced	Stones Trauma Foreign body Urethral stricture Polycystic kidneys Arteriovenous malformation Infarct Hydronephrosis Fistula	Anticoagulants Coagulation defects Sickle cell disease Thromboembolism

History

- timing of hematuria in urinary stream
  - beginning of micturition: anterior urethra
  - end of micturition: bladder neck, prostatic urethra
  - entire duration of micturition: bladder and above
- presence of blood clots
- LUTS and associated symptoms
  - pyuria, dysuria, urgency: UTI
  - flank pain, radiation to groin: ureteral obstruction
- last menstrual period, history of kidney stones, UTI, or previous urologic surgery
  - recent UTI, post-infectious glomerulonephritis, IgA nephropathy
- medications (anticoagulants, rifampin, phenazopyridine, phenytoin)
- risk factors for malignancy (smoking, chemical exposures, Hx of cyclophosphamide therapy, pelvic radiation)

Common Urologic Causes of Hematuria can be Classified as:

TICS
Trauma/**T**umour/**T**oxins
Infection/**I**nflammatory
Calculi/**C**ysts
Surgery/**S**ickle cell and other hematological causes

Investigations

- U/A, urine C&S, urine cytology
- imaging
  - lower tract: cystoscopy
  - upper tract: CTU (gold standard), U/S
- CBC (rule out anemia, leukocytosis), electrolytes, creatinine (Cr), blood urea nitrogen (BUN), INR, partial thromboplastin time (PTT), PSA (in men)

Upper Tract Imaging Options

CTU: Test of choice to evaluate the renal parenchyma and collecting system. Involves exposure to radiation and IV contrast (assess renal function and allergies)

U/S: Superior to IVP for evaluation of renal parenchyma and renal cysts; limited sensitivity for Urothelial carcinoma and small renal masses; U/S alone may be insufficient for upper tract imaging

Magnetic Resonance (MR) Urography: Evaluation of renal parenchyma, collecting system and congenital anomalies; beneficial in pediatric or pregnant patients or when ionizing radiation has to be avoided. (Assess renal function and allergies)

Acute Management of Severe Bladder Hemorrhage

- manual irrigation via catheter with normal saline to remove clots
- CBI using large (20-24 Fr) 3-way Foley to help prevent clot formation
  - should be done after manual irrigation of all clots
- cystoscopy
  - identify tumours or other source(s)
  - coagulate obvious sites of bleeding or transurethral resection of tumours (under general or regional anesthesia)

Microscopic Hematuria

Definition

- blood in the urine that is not visible to the naked eye
- >2 RBCs/HPF on urinalysis of at least two separate samples

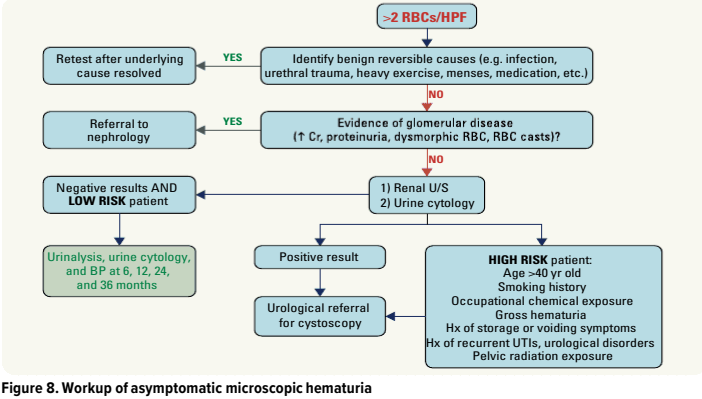
>2 RBCs/HPF
Identify benign reversible causes (e.g. infection, urethral trauma, heavy exercise, menses, medication, etc.)
YES
Retest after underlying cause resolved
NO
Evidence of glomerular disease (↑ Cr, proteinuria, dysmorphic RBC, RBC casts)?
YES
Referral to nephrology
NO
1) Renal U/S
2) Urine cytology
Negative results AND LOW RISK patient
Urinalysis, urine cytology, and BP at 6, 12, 24, and 36 months
Positive result
Urological referral for cystoscopy
HIGH RISK patient:
Age >40 yr old
Smoking history
Occupational chemical exposure
Gross hematuria
Hx of storage or voiding symptoms
Hx of recurrent UTIs, urological disorders
Pelvic radiation exposure

Figure 8. Workup of asymptomatic microscopic hematuria
Based on CUA Guidelines. Alternatively, the AUA recommends cystoscopy and CTU for all patients with confirmed microscopic hematuria; follow-up for negative workup is urinalysis yearly for two yr, with repeat anatomic evaluation if microscopic hematuria persists

Lower Urinary Tract Dysfunction

- two phases of lower urinary tract function
  1. storage phase (bladder filling and urine storage) requires:
     - accommodation and compliance
     - no involuntary contraction(s)
  2. voiding phase (bladder emptying) requires:
     - coordinated detrusor contraction
     - synchronous relaxation of outlet sphincters
     - no anatomic obstruction
- lower urinary tract dysfunction can therefore be classified as:
  - failure to store: due to bladder or outlet
  - failure to void: due to bladder or outlet
- three types of symptoms
  - storage (formerly known as irritative)
  - voiding (formerly known as obstructive)
  - post-voiding

Transient Causes of Reversible Urinary Incontinence in the Elderly

DIAPERS
Delirium
Inflammation/**I**nfection
Atrophic vaginitis/urethritis
Pharmaceuticals/**P**sychological
Excess U/O
Restricted mobility/**R**etention
Stool impaction

Urinary Incontinence

Definition

- involuntary leakage of urine

Epidemiology

- variable prevalence in women: 25-45%
- F:M=2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

Urgency is the complaint of a sudden compelling desire to void that is difficult to defer; it is not necessarily associated with incontinence

Table 3. Urinary Incontinence: Types and Treatments

Type	Stress	Urgency	Mixed	Overflow
Definition	Leakage with sudden increases in intra-abdominal pressure (cough, sneeze, exertion)	Leakage preceded by strong, sudden urge to void	Leakage with urgency and increased intra-abdominal pressure	Leakage associated with urinary retention
Etiology	Sphincter incompetence Urethral hypermobility Common in middle aged and older women, and men following prostate cancer treatment, or rarely surgical treatment of BPH	Detrusor overactivity Bladder hypersensitivity	Same as stress and urgency incontinence	BPH with overflow incontinence From weak bladder that does not empty (e.g. diabetic cystopathy)
Investigations	Hx: when leakage occurs, number of pads, LUTS, history of neurologic disease, pelvic surgery/radiotherapy, obstetrical history, bowel and sexual function, medications, impact on quality of life P/E: general (edema, neurologic abnormalities, mobility, cognition, dexterity), abdomen (distended bladder, masses, scars), GU (vaginal sizing for pessary, tissue quality, tissue sensation, vaginal examination including prolapse evaluation in women, DRE in men), cough test U/A, urine C&S, voiding diary (type of incontinence, how often, volume of leakage) Urodynamics			See *Urinary Retention, U1*
Management	Risk reduction: weight loss, smoking cessation Kegel exercises PFMT Surgery: urethral slings, or artificial sphincter in men	Conservative: fluid management, bladder training, Kegel exercises Medication: anticholinergics, β-3 agonist Botulinum toxin A bladder injection Neuromodulation	Combination of management of stress and urgency incontinence	Catheterization Treat underlying cause

Lower Urinary Tract Symptoms

Urinary Retention

- inability to pass urine voluntarily

Table 4. Etiology of Urinary Retention

Outflow Obstruction	Bladder Innervation	Pharmacologic	Infection
Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurological (DSD) Prostate: BPH, prostate cancer Urethra: stricture, phimosis, traumatic disruption Miscellaneous: constipation, pelvic mass, severe prolapse in women	Intracranial: CVA, tumour, Parkinson's, cerebral palsy Spinal cord: injury, disc herniation, MS DM Post-abdominal or pelvic surgery	Anticholinergics Narcotics Antihypertensives (ganglionic blockers, methyldopa) OTC cold medications containing ephedrine or pseudoephedrine Antihistamines Psychosomatic substances (e.g. MDMA (ecstasy))	GU: UTI, prostatitis, abscess, genital herpes Infected foreign body Varicella zoster

If a trauma patient is unable to void, has blood at urethral meatus, a scrotal hematoma, or a high riding prostate, there is urethral injury until proven otherwise so catheterization is CONTRAINDICATED unless performed by urology staff or resident

Clinical Features

- suprapubic pain (with acute retention), incomplete emptying, weak stream
- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal discharge (with UTI)
- increased size of prostate or reduced anal sphincter tone (with neurological disease) on DRE
- storage symptoms: frequency, urgency (strong need to void), nocturia (FUN)
- voiding symptoms: stream changes/straining, hesitancy, incomplete emptying, post-void dribbling (SHED)
- neurological: presence of abnormal or absent deep tendon reflexes, reduced "anal wink," saddle anesthesia

Acute vs. Chronic Retention
Acute retention is a medical emergency characterized by suprapubic pain and inability to void
Chronic retention can be painless with greatly increased bladder volume and detrusor hypertrophy followed by atony (late)

Investigations

- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

Patients with ascites may have a falsely elevated PVR measured by bladder scan

Treatment

- treat underlying cause
- catheterization
  - acute retention
    - immediate catheterization to relieve retention; leave Foley in to drain bladder; follow-up to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - intermittent catheterization by patient may be used. Definitive treatment depends on etiology
- suprapubic catheter if obstruction precludes urethral catheter
- for postoperative patients with retention:
  - encourage ambulation
  - α-blockers to relax bladder neck/outlet (men only)
  - may need catheterization
  - definitive treatment will depend on etiology
  - minimize narcotic use
  - ensure good bowel function (i.e. treat constipation)

Benign Prostatic Hyperplasia

Definition

- proliferation of epithelial tissue, connective tissue, and smooth muscle in the prostatic transition zone

Etiology

- unknown
  - DHT required (converted from testosterone by 5-α reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors

Epidemiology

- age-related, extremely common (50% of 50 y/o, 80% of 80 y/o)
- 25% of men will require treatment

Clinical Features

- result from outlet obstruction and compensatory and/or age-related changes in detrusor function
- voiding and storage symptoms
- DRE
  - prostate is smooth, rubbery, and may be symmetrically enlarged

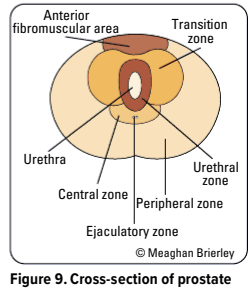

Figure 9. Cross-section of prostate

Prostate size does not correlate well with symptoms in BPH

- complications
  - retention
  - overflow incontinence
  - hydronephrosis
  - renal insufficiency
  - infection
  - gross hematuria
  - bladder stones

Investigations
- mandatory: Hx including LUTS, surgery, trauma, medications (OTC and phytotherapeutic agents), impact of QOL, P/E including DRE, U/A to exclude UTI
- recommended: symptom inventory (IPSS or AUA-Symptom Index (SI)), PSA if >10 yr life expectancy or if it changes management of LUTS
- optional: Cr, urine cytology, uroflowmetry, PVR, voiding diary, sexual function questionnaire
- renal U/S to assess for hydronephrosis
- consider cystoscopy or bladder ultrasound prior to potential surgical management to evaluate outlet and prostate volume
- biopsy if suspicious for malignancy, i.e. elevated PSA or abnormal DRE

Treatment

Table 5. Treatment of BPH (see Table 28, U47, Figure 6, U3, and Figure 7, U4)

	Conservative	Medical	Surgical	Minimally Invasive Surgical Therapies
When to use	Asymptomatic or mildly symptomatic, minimal bother	Moderately to severely symptomatic, bothersome	Absolute or relative indications, significant bother	Patients who wish to avoid or may not tolerate surgery
Options	Watchful waiting: 50% of patients improve spontaneously Lifestyle modifications (e.g. evening fluid restriction, planned voiding)	α-adrenergic antagonists: reduce smooth muscle tone (neck of bladder, prostate, urethra) 5-α reductase inhibitor: block conversion of testosterone to DHT; act to reduce prostate size Combination of α-adrenergic antagonists and 5-α reductase inhibitor is synergistic Antimuscarinics or β-3 agonist (for storage LUTS, without elevated PVR) PDE5 inhibitors (ED and for storage and voiding LUTS) Desmopressin (LUTS with nocturia); risk of hyponatremia in ≥65 yr	TURP (see U45) BPKVP (<60 cc) Laser prostatectomy TUIP (<30 cc) Aquablation (<80 cc) Open or Robotic Assisted Laparoscopic simple prostatectomy (>100 cc)	TUMT UroLift (<80 cc) Convective water vapour energy ablation (Rezum™) Prostatic stent (for those unfit for surgery) Prostatic Artery Embolization

Urethral Stricture

Definition
- decrease in urethral caliber due to scar formation in urethra
- M>F

Etiology
- idiopathic
- iatrogenic
- congenital
  - failure of normal canalization (e.g. posterior urethral valves)
- trauma
  - instrumentation (e.g. cystoscopy, TURP)/catheterization (most common)
  - external trauma (e.g. burns, straddle injury, urethral injury from pelvic fracture)
  - foreign body
  - prostate cancer therapy (radical prostatectomy, radiation therapy)
- infection
  - long-term indwelling catheter
  - STI (gonococcal or chlamydial disease)
- inflammation
  - balanitis xerotica obliterans (BXO; lichen sclerosus or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal and urethral stenosis
  - radiation
- malignancy (urothelial carcinoma)
  - most urethral cancers in men are squamous (vs. prostate, bladder, or upper tract that are mostly transitional cell in origin)

Approximate Prostate Sizes
20 cc – chestnut
25 cc – plum
50 cc – lemon
75 cc – orange
300 cc – grapefruit

AUA BPH Symptom Score

FUNWISE
Frequency
Urgency
Nocturia
Weak stream
Intermittency
Straining
Emptying, incomplete feeling of

Each symptom graded out of 5
0-7: Mildly symptomatic
8-19: Moderately symptomatic
20-35: Severely symptomatic
Note: dysuria not included in score but is commonly associated with BPH

Initial α-adrenergic antagonist monotherapy for score <20, combination therapy for score >20 (type of medication is size-dependent; 5-α reductase inhibitor beneficial with larger prostates)

Men with planned cataract surgery should avoid starting α-adrenergic antagonists until after their surgery due to the risk of intraoperative floppy iris syndrome

BPH Surgery

Absolute Indication
Renal failure with obstructive uropathy
Refractory urinary retention

Relative Indications
Recurrent UTIs
Recurrent hematuria refractory to medical treatment
Renal insufficiency (rule out other causes)
Bladder stones
Severe symptoms unresponsive to medical therapies

Clinical Features
- voiding and storage symptoms ± gross hematuria
- urinary retention
- hydronephrosis
- related infections: recurrent UTI, secondary prostatitis/epididymitis

Investigations
- laboratory findings
  - flow rates <10 mL/s (normal >15 mL/s) on uroflowmetry
  - urine culture usually negative, but U/A may show pyuria
- radiologic findings
  - RUG and VCUG will demonstrate location
- cystoscopy

Treatment
- urethral dilatation
  - temporarily increases lumen size by breaking up scar tissue
  - healing will often reform scar tissue, recurrence of stricture
- VIU
  - endoscopically incise stricture
  - equal success rates to dilation with mid bulbar strictures <2 cm
  - high rate of recurrence (30-80%), avoid in younger patients
- open surgical reconstruction (urethroplasty)
  - complete stricture excision with anastomosis depending on location and size of stricture
  - may require graft to reconstruct (e.g. buccal mucosa)
  - higher long-term success rate than urethral dilatation or visual internal urethrotomy
  - urethrostomy may also be considered as an alternative to urethroplasty in certain patients

Neurogenic Bladder

Definition
- dysfunction of the urinary bladder due to deficiency in some aspect of its innervation, often presents with overflow incontinence and urgency incontinence

Neurophysiology
- see *Figure 6, U3* and *Figure 7, U4*
- stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  - micturition (voiding)
  - stimulation of parasympathetic neurons (bladder contraction)
  - inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  - voluntary relaxation of the pelvic floor and striated urethral sphincter
  - urine storage
  - opposite of micturition
- voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
- cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem to inhibit the detrusor reflex

Examples of Neurogenic Lower Urinary Tract Dysfunction
- neurogenic detrusor overactivity (NDO; formerly termed detrusor hyperreflexia)
  - lesion above PMC (e.g. stroke, tumour, MS, Parkinson's disease)
  - loss of voluntary inhibition of voiding
  - intact pathway inferior to PMC maintains coordination of bladder and sphincter
- DSD
  - suprasacral lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  - loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  - component of detrusor overactivity as well
- detrusor atony/areflexia
  - lesion of sacral cord or peripheral nerves (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality, post abdominoperineal resection)
  - flaccid bladder which fails to contract
  - may progress to poorly compliant bladder with high pressures
- peripheral autonomic neuropathy
  - deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
- muscular lesion
  - can involve detrusor, smooth/striated sphincter

Combination Therapy vs. α-Blocker or 5ARI
BJU Int 2011;107(6):946-54
Purpose: To compare the incidence of acute urinary retention, benign prostatic hyperplasia (BPH)-related surgery and overall clinical progression in patients treated with tamsulosin, dutasteride, and combination therapy.
Methods: 4 yr combination of dutasteride and tamsulosin study was a multicentre double-blind RCT of outcomes in men ≥50 yr with symptomatic BPH, with PSA ≥1.5 ng/mL and ≤10 ng/mL, and prostate volume ≤30 mL. Patients received tamsulosin, dutasteride or combination therapy. Primary endpoint was time to first acute urinary retention or BPH-related surgery; secondary endpoint was clinical progression of BPH/symptoms.
Results: Combination therapy resulted in significantly greater improvements in symptoms compared to dutasteride from 3 mo, and tamsulosin from 9 mo, and in BPH-related health status from 3 and 12 mo, respectively. There was a significant increase in Adverse Drug Events (ADE) with combination therapy vs. monotherapies. However, withdrawal rates due to drug-related adverse events were similar across the treatment groups.
Conclusions: Men with baseline prostate volume ≥40 mL and baseline PSA ≥1.5 ng/mL had greater reductions in relative risk (RR) of BPH-related surgery and RR of clinical progression on combined therapy or dutasteride monotherapy than on tamsulosin monotherapy.

Finasteride for Benign Prostatic Hyperplasia
Cochrane DB Syst Rev 2010;10:CD006015
Purpose: To examine the effectiveness and safety of finasteride vs. placebo or other active controls for the treatment of urinary tract symptoms.
Summary of Findings:
1. Finasteride improved urinary symptoms more than placebo in trials >1 yr duration and significantly lowered the risk of BPH progression.
2. Compared with α-blockers, finasteride was less effective than either doxazosin or terazosin, but equally as effective as tamsulosin.
3. Symptom improvement with finasteride + doxazosin is equal to doxazosin alone.
4. Finasteride treatment resulted in an increased risk of ejaculation disorder, impotence, and lowered libido compared with placebo.
5. Compared with doxazosin and terazosin, finasteride had a lower risk of asthenia, dizziness, and postural hypotension.

Nerve roots in micturition:
"S2-3-4 keeps the urine off the floor"

Neuro-Urologic Evaluation

"Spinal shock" initially manifests as atonic bladder

- Hx and P/E (urologic and general neurologic)
- voiding diary, assess for incontinence, urinary symptoms, and UTI risk (hydration status, catheterization, voiding frequency)
- catheterization volumes in patients with CIC
- all patients: U/A, PVR, renal profile
  - moderate/high-risk (spinal cord injury, spina bifida, MS): urodynamics, renal U/S, renal profile
- imaging
  - U/S to rule out hydronephrosis and stones; occasionally CT scanning with or without contrast
- cystoscopy (if suspicion of bladder tumour, hematuria)
- urodynamic studies
  - uroflowmetry to assess flow rate, pattern
  - filling CMG to assess capacity, compliance, detrusor overactivity
  - voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
  - video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
  - EMG and video ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

Treatment

- goals of treatment
  - prevent renal deterioration
  - prevent infections (UTI)
  - achieve social continence
- CIC (if there is associated inability to void)
- treatment options depend on status of bladder and urethra
  - bladder hyperactivity → antimuscarinic medications to relax bladder (see *Urinary Incontinence, U6*)
    - if refractory
      - botulinum toxin injections into bladder wall (detrusor muscle)
      - occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      - occasionally urinary diversion (ileal conduit or continent diversion) in severe cases if bladder management unsuccessful
  - flaccid bladder → CIC

Dysuria

Definition

- painful urination

Etiology

Table 6. Differential Diagnosis of Dysuria

Infectious	Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perineal inflammation/infection, tuberculosis, vestibulitis
Neoplasm	Kidney, bladder, prostate, penis, vagina/vulva, BPH
Calculi	Bladder stone, urethral stone, ureteral stone
Inflammatory	Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis
Hormonal	Endometriosis, hypoestrogenism
Trauma	Catheter insertion, post-coital cystitis (honeymoon cystitis)
Psychogenic	Somatization disorder, depression, stress/anxiety disorder
Other	Contact sensitivity, foreign body, radiation/chemical cystitis, diverticulum

Investigations

- focused Hx and P/E to determine cause (fever, d/c, conjunctivitis, CVA tenderness, back/joint pain)
  - any d/c (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal d/c
  - U/A and urine C&S
  - if suspect infection, may start empiric ABx treatment (see *Table 9, U16*)
  - ± imaging of urinary tract (tumour, stones)

Hydronephrosis

Definition
- the upper urinary tract consists of the kidneys and ureters
- dilation of the renal pelvis, calyces, and ureters, generally caused by obstruction of antegrade urine flow (i.e. pelvicaliectasis)

Etiology
- mechanical
  - congenital: see *Congenital Abnormalities, U39*
  - acquired
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, ureteral or urethral stricture, phimosis, previous urological surgery
    - extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
- functional
  - neuropathic: neurogenic bladder, diabetic neuropathy, spinal cord disease
  - hormonal: pregnancy (progesterone decreases ureteral tone)

Investigations
- focused Hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, Hx of UTIs, calculi, PID, and urological surgery
- CBC, electrolytes, Cr, BUN, U/A, urine C&S
- imaging studies (U/S is >90% sensitive and specific)
  - CT: helps delineate anatomy and potential causes (e.g. obstructing stone), but does not provide much functional information
  - mercaptoacetyltriglycine (MAG3) diuretic renogram: provides little anatomic/structural information, but evaluates differential renal function and demonstrates if functional obstruction exists (i.e. delayed drainage of radiotracer)
  - retrograde pyelogram: helps to delineate anatomy and can allow for stent insertion to decompress if obstruction is present

Treatment
- hydronephrosis can be physiologic (e.g. pregnancy)
- treatment should be guided at improving symptoms, treating infections, or improving renal function
- urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure
- treatment can include pyeloplasty to repair an obstructed UPJ in congenital or acquired UPJ obstruction

Post-Obstructive Diuresis

Definition
- polyuria resulting from relief of obstructive uropathy (i.e. elevated Cr)
- >3 L/24 h or >200 cc/h for two consecutive h

Pathophysiology
- physiologic POD secondary to excretion of retained urea, Na^+, and H_2O (high osmotic load) after relief of obstruction
  - self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
- pathologic POD is a Na^+-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to:
  - decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  - increased medullary blood flow (solute washout)
  - increased flow and solute concentration in the distal nephrons

Management
- admit patient and closely monitor hemodynamic status and electrolytes (Na+ and K+ q6-12 h and replace prn; follow Cr and BUN to baseline)
- monitor U/O q2 h and ensure total fluid intake <U/O by replacing every 1 mL U/O with 0.5 mL 1/2 normal saline (NS) IV (PO fluids if physiologic POD)
- avoid glucose-containing fluid replacement (iatrogenic diuresis)

Overactive Bladder

Definition
- a symptom complex that includes urinary urgency with or without incontinence, urinary frequency (voiding ≥8 times in a 24 h period), and nocturia (awakening one or more times at night to void)

Etiology
- multiple etiologies proposed (neurogenic, myogenic, idiopathic)
- symptoms thought to be from involuntary contractions of the detrusor muscle
- may be associated with other conditions such as SUI in women and BPH in men (see *Table 5, U8*)

Epidemiology
- F:M=1:1
- prevalence increases with age. 42% in males ≥75 y/o; 31% in females ≥75 y/o
- women experience incontinence more commonly than men

Diagnosis
- the diagnostic process should document symptoms that define overactive bladder and exclude other disorders that could cause the patient's symptoms
- minimal requirements for the process consist of:
  - focused history including past genitourinary disorders and conditions outlined in *Table 7*, questionnaires of LUTS and diaries of urination frequency, volume and pattern (3 d micturition diary)
  - P/E including genitourinary, pelvic, and rectal examination
  - U/A to rule out hematuria and infection
- in some patients, the following investigations could be considered
  - post-void residual
  - cystoscopy to rule out recurrent infections, carcinoma in situ and other intravesical abnormalities
- urodynamics to rule out obstruction in older men

Treatment
- non-pharmacological: behaviour therapies such as bladder training, bladder control strategies, pelvic floor muscle training, fluid management, weight reduction (if overweight), and avoidance of caffeine and alcohol
- pharmacological (see *Table 29, U48*)
  - antimuscarinics: oxybutynin hydrochloride, tolterodine, solifenacin, fesoterodine, darifenacin, propiverine, or trospium
  - β3-adrenoceptor agonist: mirabegron
- refractory patients may be treated with:
  - neuromuscular-junction inhibition: botulinum toxin bladder injection
- others
  - percutaneous tibial nerve stimulation (not used commonly in Canada)
  - sacral neuromodulation

Table 7. Conditions that Could Contribute to Symptoms of Overactive Bladder

Lower Urinary Tract Conditions	UTI, obstruction, impaired bladder contractility
Neurological Conditions	Stroke, MS, dementia, diabetic neuropathy
Systemic Diseases	CHF, sleep disorders (primarily nocturia)
Functional and Behavioural	Excessive caffeine and alcohol, constipation, impaired mobility
Medication	Diuretics, anticholinergic agents, narcotics, calcium-channel blocker, cholinesterase inhibitors

Infectious and Inflammatory Diseases

Table 8. Antibiotic Treatment of Urological Infections

Condition	Drug	Duration
Urethritis	**Non-Gonococcal**	
	azithromycin (1 g PO)	x 1 d
	OR	
	doxycycline (100 mg PO BID)	7 d
	Gonococcal	
	ceftriaxone (250 mg IM) AND treat for *Chlamydia trachomatis*	x 1
Simple, Uncomplicated UTI	TMP/SMX (160 mg/800 mg PO BID)	3 d
	OR	
	nitrofurantoin (100 mg PO BID)	5 d
Complicated UTI	ciprofloxacin (1 g PO once daily OR 400 mg IV q12 h)	up to 2-3 wk
	OR	
	ampicillin (1 g IV q6 h) + gentamicin (1 mg/kg IV q8 h) (used for relatively short courses because of toxicity)	up to 2-3 wk
	OR	
	ceftriaxone (1-2 g IV q24 h)	up to 2-3 wk
Recurrent/Chronic Cystitis	Prophylactic Treatment	
	Continuous: TMP-SMX (40 mg/200 mg PO QHS OR 3x/wk)	6-12 mo
	OR	
	nitrofurantoin (50-100 mg PO QHS)	6-12 mo
	Post-Coital: TMP-SMX (40 mg/200 mg-80 mg/400 mg)	within 2 h of coitus
	OR	
	nitrofurantoin (50-100 mg PO once daily)	within 2 h of coitus
Acute Prostatitis	ciprofloxacin (500-750 mg PO BID)	2-4 wk
	OR	
	TMP-SMX (160 mg/800 mg PO BID)	4 wk
	OR	
	IV therapy with gentamicin and ampicillin, penicillin with β-lactamase inhibitor, 3rd gen cephalosporin, OR a fluoroquinolone	4 wk (IV and oral step-down)
Chronic Prostatitis	ciprofloxacin (500 mg PO BID) ± α-blockers, anti-inflammatories	4-6 wk
Epididymitis/Orchitis	<35 yr (presumed STI) ceftriaxone (200 mg IM)	x 1
	AND	
	doxycycline (100 mg PO BID)	10 d
	≥35 yr (presumed urinary source)	
	ofloxacin (300 mg PO BID)	10 d
Acute Uncomplicated Pyelonephritis	ciprofloxacin (500 mg PO BID)	7 d
	± ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV)	x 1
	OR	
	IV therapy with a fluoroquinolone, gentamicin and ampicillin, extended spectrum cephalosporin, extended spectrum penicillin, OR a carbapenem	14 d total IV and oral step-down

Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results

Acute uncomplicated pyelonephritis: suspected or confirmed *Enterococcus* infection requires treatment with ampicillin

Urinary Tract Infection

• for UTIs during pregnancy, see Obstetrics, OB13

Definition

• symptoms suggestive of UTI + evidence of pyuria and bacteriuria on U/A or urine C&S
  ▪ if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy, immunosuppressed, prior to urologic surgery)

Classification

• uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
• complicated: structural and/or functional abnormality, male patients, immunocompromised, diabetic, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
• recurrent: see *Recurrent/Chronic Cystitis, U14*

Risk Factors

• stasis and obstruction
  ▪ residual urine due to impaired urine flow (e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder)
• foreign body
  ▪ introduce pathogen or act as nidus of infection (e.g. catheter, instrumentation)
• decreased resistance to organisms
  ▪ DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
• other factors
  ▪ trauma, anatomic abnormalities, female, sexual activity, menopause, fecal incontinence

Clinical Features
- storage symptoms: frequency, urgency
- voiding symptoms: hesitancy, post-void dribbling, dysuria
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

Indications for Investigations
- pyelonephritis
- persistence of pyuria/symptoms following adequate antibiotic therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- Hx of structural abnormalities/decreased flow

Investigations
- U/A, urine C&S (only if symptomatic)
  - U/A: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see *Microscopic Hematuria, U5*)
- U/S, CT scan if recurrent or treatment-resistant UTIs, suspected anatomic abnormalities, history indicates complicated cystitis
- pelvic examination for women if recurrent UTI

Treatment
- see *Table 8, Antibiotic Treatment of Urological Infections, U13*
- asymptomatic bacteriuria should not be treated (exceptions: pregnancy, before urological procedure)
- if febrile, consider admission with IV therapy and rule out obstruction

Prevention of UTIs
- maintain good hydration (emerging evidence re: cranberry preparations and D-mannose)
- void regularly (do not hold urine for prolonged periods of time)
- avoid feminine hygiene sprays and scented douches
- empty bladder immediately before and after intercourse
- vaginal estrogen therapy for peri- and post-menopausal women with recurrent UTIs, particularly with evidence of atrophic vaginitis
- future directions: UTI vaccines on the horizon

Organisms
- typical organisms: SEEK PP (*E. coli* 75-95%)
- atypical organisms
  - tuberculosis (TB)
  - *Chlamydia trachomatis*
  - *Mycoplasma (Ureaplasma urealyticum)*
  - fungi (*Candida*)

Recurrent/Chronic Cystitis

Definition
- ≥3 UTIs/yr or ≥2 UTIs per six mo

Etiology
- bacterial reinfection (80%) vs. bacterial persistence (relapse)
  - bacterial reinfection
    - recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  - bacterial persistence
    - same organism cultured within 2 wk of sensitivity-based therapy

Investigations
- assess predisposing factors
- investigations may include cystoscopy, U/S, CT

Treatment
- lifestyle changes (limit caffeine intake, increase fluid/H2O intake)
- ABx (various strategies): continuous low-dose daily suppression vs. post-coital only vs. self-start therapy
- post-menopausal women: consider topical estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

Interstitial Cystitis (Painful Bladder or Bladder Pain Syndrome)

Definition
- bladder pain, chronic urgency, and frequency without other identifiable causation

Classification
- non-ulcerative (more common) and ulcerative (Hunner's lesions)

Etiology
- unknown

Epidemiology
- prevalence: 20 in 100,000
- 90% of cases are in females, 94% are white
- median age is 40 yr (non-ulcerative seen in younger to middle-aged, while ulcerative seen in middle-aged to older)

Clinical Features
- pelvic pain (typically supra-pubic tenderness)
- storage symptoms (frequency > urgency > nocturia)
- negative U/A, urine C&S, urine cytology
- cystoscopy: glomerulations (submucosal petechiae), Hunner's lesions

Cystoscopic evaluation is not necessary to make a diagnosis

Differential Diagnosis
- urology: non-infectious cystitis (radiation, chemical, eosinophilic, TB), OAB, bladder calculi, prostate-related pain
- gynecology: endometriosis, vulvar disorders
- neurology: pudendal nerve entrapment
- MSK: pelvic floor disorders
- drugs: ketamine, tiaprofenic acid

Investigations
- Hx, P/E, frequency volume chart
- symptom scores to establish baseline and response to treatment
- U/A, urine C&S, urine cytology
- cystoscopy

Treatment
- first line: patient education, dietary modifications, bladder retraining, stress management
  - pelvic floor physiotherapy can be added for patients with pelvic floor dysfunction or pelvic pain
- second line: guided by symptom phenotype
  - oral: amitriptyline, cimetidine, hydroxyzine, pentosan polysulfate (PPS), gabapentin, quercetin
  - intravesical: dimethylsulfoxide, heparin, lidocaine, PPS, oxybutynin
- third line: hydrodistension, botulinum toxin A, sacral neuromodulation
  - endoscopic treatment if Hunner's lesions (cauterization, resection, triamcinolone injection)
- fourth line: radical surgery (substitution cystoplasty or urinary diversion ± cystectomy)

Acute Pyelonephritis

Definition
- infection of the renal parenchyma with local and systemic manifestations
- clinical diagnosis of flank pain, fever, and elevated WBC

Etiology
- ascending from lower UTI (usually Gram-negative bacilli) or hematogenous route (usually Gram-positive cocci)
- causative microorganisms
  - Gram positives: *Enterococcus faecalis, S. aureus, S. saphrophyticus*
  - Gram negatives: *E. coli, Klebsiella, Proteus, Pseudomonas, Enterobacter*
- common underlying causes of pyelonephritis
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

Clinical Features
- rapid onset (<24 h)
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness and/or exquisite flank pain

Investigations
- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging if complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

Treatment
- hemodynamically stable
  - outpatient oral ABx treatment ± single initial IV dose (see *Table 8, U13*)
- severe or non-resolving
  - admit, hydrate, and treat with IV ABx (see *Table 8, U13*)
- emphysematous pyelonephritis
  - most patients receive nephrectomy after IV ABx started and patient stabilized
  - consider temporization with nephrostomy tubes
- renal obstruction
  - admit for emergent stenting or percutaneous nephrostomy tube

Prostatitis/Prostatodynia

Epidemiology
- prevalence: 9% of men/yr, 6% with bothersome symptoms
- most common urologic diagnosis in men <50 y/o, 3rd most common in men >50 y/o

Classification

Table 9. Comparison of the Four Types of Prostatitis

	Acute Bacterial Prostatitis (Category I)	Chronic Bacterial Prostatitis (Category II)	Chronic Pelvic Pain Syndrome (Category III)	Asymptomatic Prostatitis (Category IV)
Etiology	Acute infection SEEK PP (80% *E. coli*)	Chronic infection ± prostatitis symptoms	Symptoms without evidence of infection IIIA: inflammatory IIIB: non-inflammatory	Incidental inflammation
Clinical Features	LUTS, pelvic pain Systemic signs: fever, chills, malaise Leukocytosis in prostatic fluid Positive bacterial cultures	LUTS, pelvic pain No systemic signs Recurrent UTIs Leukocytosis in prostatic fluid Positive bacterial cultures	LUTS, pelvic pain IIIA: leukocytosis in prostatic fluid IIIB: no leukocytosis in prostatic fluid	No symptoms Leukocytosis in prostatic fluid
Investigations	Hx, P/E (abdominal, external genitalia, perineum, prostate) U/A, urine C&S TRUS if suspect abscess	Hx, P/E (same as Category I + pelvic floor) 4 glass test for culture: VB1 (urethra) VB2 (bladder) EPS (post-massage) VB3 (post-massage)	Hx, P/E (same as Category II) Symptom score (NIH-CPSI*) 4-glass test Consider psychological assessment	No investigations unless considering ABx for elevated PSA or infertility
Treatment	ABx (see *Table 8, U13*) Catheterization if severe obstructive Drainage if abscess is present	ABx (see *Table 8, U13*) α-blocker if obstruction	Supportive measures ABx if ABx naïve Multimodal therapy (UPOINT), including: α-blockers Anti-inflammatories Phytotherapy (quercetin, cernilton)	ABx if elevated PSA, infertility, or planned prostate biopsy

*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index

Epididymitis and Orchitis

Etiology
- common infectious causes
  - <35 yr: *Neisseria gonorrhoeae* or *Chlamydia trachomatis*
  - ≥35 yr or penetrative anal intercourse: GI organisms (especially *E. coli*)
- other causes
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)
  - chemical: reflux of urine into ejaculatory ducts

Risk Factors
- UTI
- unprotected sexual contact
- instrumentation/catheterization
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis
- immunocompromised

If unsure between diagnoses of epididymitis and torsion, always go to OR
Remember: torsion >6 h has poor prognosis

Clinical Features
- sudden onset scrotal pain and swelling ± radiation along cord to flank
- scrotal erythema and tenderness
- Prehn's Sign (relief of pain with lifting of testicle)
- fever
- storage symptoms, purulent d/c
- reactive hydrocele

Investigations
- U/A, urine C&S
- ± urethral d/c: Gram stain/culture
- if diagnosis uncertain, MUST rule out testicular torsion (U/S Doppler)
- U/S can confirm diagnosis with increased vascularity

Treatment
- rule out torsion (see *Table 23, Investigations, U32*)
- see *Table 8, U13 for ABx therapy*
- scrotal support, bed rest, ice, analgesia

Complications
- if severe → testicular atrophy
- 30% have persistent infertility problems
- inadequately treated acute epididymitis may lead to chronic epididymitis or epididymo-orchitis

Urethritis

Etiology
- infectious or inflammatory (e.g. reactive arthritis)

Reactive Arthritis (formerly known as Reiter's syndrome)
Urethritis, uveitis (or conjunctivitis), and arthritis
(can't pee, can't see, can't climb a tree)

Table 10. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

	Gonococcal	Non-Gonococcal
Causative Organism	*Neisseria gonorrhoeae*	Usually *Chlamydia trachomatis*
Diagnosis	Hx of sexual contact, thick, profuse, yellow-grey purulent d/c, LUTS Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen	Hx of sexual contact, mucoid whitish purulent d/c, ± storage LUTS Gram stain demonstrates >4 PMN/oil immersion field, no evidence of *N. gonorrhoeae*, urine PCR and/or culture from urethral specimen
Treatment	See *Table 8, U13*	See *Table 8, U13*

If culture negative or unresponsive to treatment consider: *Ureaplasma urealyticum, Mycoplasma genitalium, Trichimonas vaginalis*, HSV, or adenovirus

Stone Disease

Epidemiology
- prevalence: ~8% and increasing
- M:F=2:1
- peak incidence 30-50 yr of age
- recurrence rate: 10% at 1 yr, 50% at 5 yr, 60-80% lifetime
- calcium oxalate most common stone type; others include uric acid, struvite, calcium phosphate, cystine, etc.

Risk Factors
- hereditary: RTA, glucose-6-phosphate dehydrogenase deficiency, cystinuria (defect in the proximal renal tubular reabsorption of cystine), COLA syndrome (defect in resorption of cystine, ornithine, lysine and arginine), xanthinuria, hyperoxaluria, etc.
- lifestyle: minimal fluid intake (most common risk factor); excess vitamin C, oxalate, purines, calcium; living or working in extreme heat
- medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, zonisamide, indinavir, acyclovir, sulfadiazine, triamterene
- medical conditions: UTI (with urea-splitting organisms: *Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*), myeloproliferative disorders, inflammatory bowel disease, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI >30)
- bladder stones: bladder outlet obstruction, catheters, neurologic disease, DM (requires different management)

Key Points in Stone Hx
- Diet (especially FLUID INTAKE)
- Predisposing medical conditions
- Predisposing medications
- Previous episodes/investigations/ treatments
- FMHx (1st degree relative)

Clinical Features
- urinary obstruction → upstream distention → pain
  - flank pain from renal capsular distention (non-colicky)
  - severe waxing and waning pain that can radiate from flank to groin, testis, or tip of penis from distended collecting system or ureter (ureteral colic)
- writhing, persistent discomfort, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency) if the stone is in the lower ureter near the ureterovesical junction
- bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
- if fever, rule out concurrent pyelonephritis and/or obstruction
- can also present incidentally, without any pain or symptoms

The Four Narrowest Passage Points for Upper Tract Stones
- UPJ
- Pelvic brim
- Under vas deferens/broad ligament
- UVJ

Table 11. Differential Diagnosis of Renal Colic

GU	Abdominal	Neurological
Pyelonephritis Ureteral obstruction from other cause: UPJ obstruction, clot colic secondary to gross hematuria, sloughed papillae Gynecological: ectopic pregnancy, torsion/ rupture of ovarian cyst, PID	Abdominal aortic aneurysm (AAA) Bowel ischemia Pancreatitis Other acute abdominal crisis (appendicitis, cholecystitis, diverticulitis)	Radiculitis (L1): herpes zoster, nerve root compression Neuromuscular (MSK) back pain

Location of Stones
- calyx: may cause flank discomfort, persistent infection, persistent hematuria, but if non-obstructive, likely remains asymptomatic
- pelvis: tend to cause obstruction at UPJ, may cause persistent infection
- ureter: <5 mm diameter will pass spontaneously in 75% of patients but can do so with varying degrees of pain

	Radiopaque	Radiolucent
KUB	Calcium	Uric acid
	Struvite	Indinavir
	Cystine	Atazanavir
CT	Calcium	Indinavir
	Struvite	Atazanavir
	Cystine	
	Uric acid	

Stone Pathogenesis
- supersaturation of stone constituents (at appropriate temperature and pH)
- stasis, low flow, and low volume of urine (dehydration)
- crystal formation and stone nidus
- loss of inhibitory factors
  - citrate (forms soluble complex with calcium)
  - magnesium (forms soluble complex with oxalate)
  - pyrophosphate
  - Tamm-Horsfall glycoprotein

Approach to Renal Stones

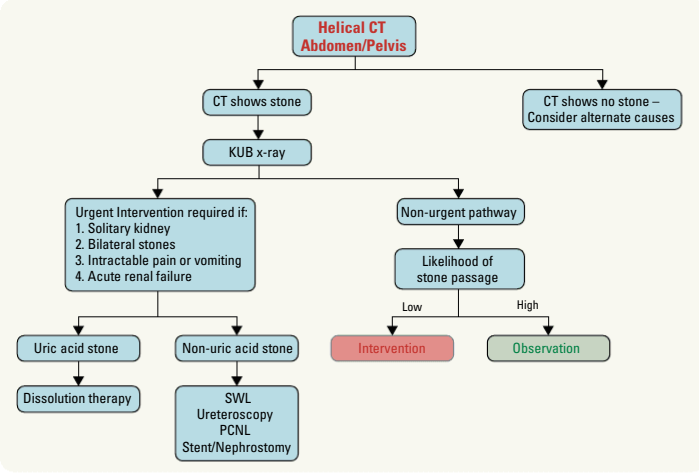

Figure 10. Approach to renal stones

Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased GI oxalate absorption and higher urine levels of calcium oxalate

Stones and Infection
If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared

Indications for PCNL
Size >2 cm
- Staghorn
- UPJ obstruction with correction of obstruction
- Calyceal diverticulum
- Large cystine stones (poorly fragmented with SWL)
- Anatomical abnormalities preventing retrograde access
- Failure of less invasive modalities

Investigations

Table 12. Investigations for Renal Stones

	CBC, U/A, Urine C&S	KUB x-ray	CT Scan (non-contrast)	Abdominal Ultrasound	Cystoscopy	Uric Acid	PTH, 24 h urine x 2 for volume, Cr, Ca^{2+}, Na^{+}, PO_4^{3-}, Mg^{2+}, oxalate, citrate, ± cystine
Who gets it?	Everyone	Most	First episode renal colic	Pediatric cases, pregnant patients, recurrent stone formers, unsure of Dx	Those concerning for bladder stone	Stone not seen on KUB	Recurrent Ca^{2+}stone formers ± pediatric cases
Why is it done?	May show signs of infection, ± sensitivities	90% of stones are radiopaque Good for follow-up Helps rule out uric acid stones (not visible on x-ray)	Able to see adjacent organs, exact location of stone(s), plan for surgery, etc. Can assess density of stone Gold standard diagnostic test	Identify and follow up stone without radiation exposure Visualize hydronephrosis	Visualize bladder Can provide access to ureter for stent placement if needed	Suspected uric acid stone (urine pH <5.5 might suggest uric acid stone)	Need to rule out metabolic cause for stones
Cautions	Presence of leukocytes NOT always indicative of infection	Not all stones visible on x-ray Do not mistake phleboliths for stones!	Radiation (especially if female of child bearing age) Must be a non-contrast scan	–	–	–	–

Treatment

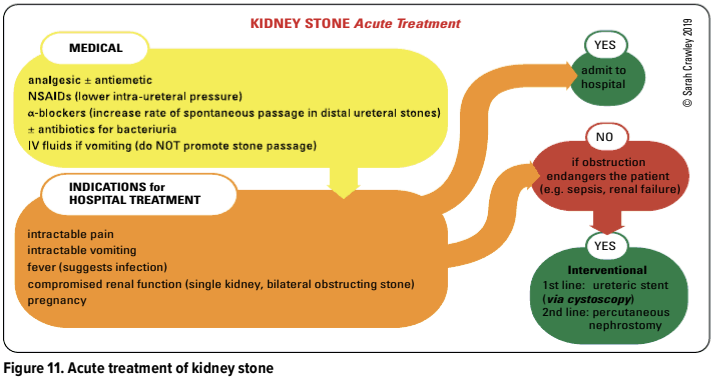

Figure 11. Acute treatment of kidney stone

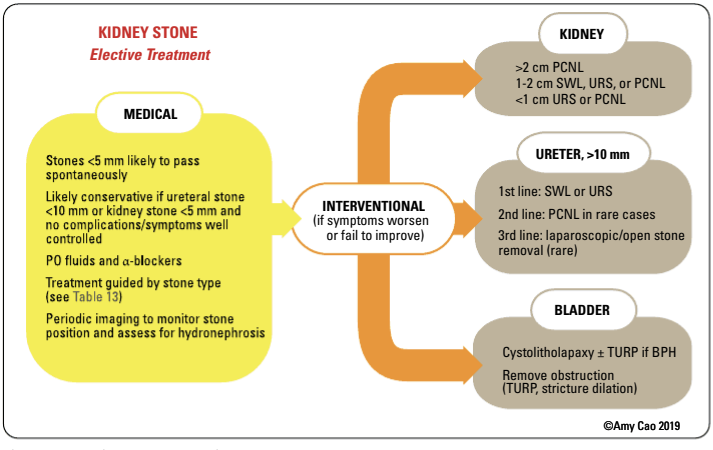
KIDNEY STONE
Elective Treatment
MEDICAL
Stones <5 mm likely to pass spontaneously
Likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
PO fluids and α-blockers
Treatment guided by stone type (see Table 13)
Periodic imaging to monitor stone position and assess for hydronephrosis
INTERVENTIONAL
(if symptoms worsen or fail to improve)
KIDNEY
>2 cm PCNL
1-2 cm SWL, URS, or PCNL
<1 cm URS or PCNL
URETER, >10 mm
1st line: SWL or URS
2nd line: PCNL in rare cases
3rd line: laparoscopic/open stone removal (rare)
BLADDER
Cystolitholapaxy ± TURP if BPH
Remove obstruction (TURP, stricture dilation)
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Figure 12. Elective treatment of kidney stone

α-Blockers as Medical Expulsive Therapy for Ureteral Stones
Cochrane DB Syst Rev 2018;4:CD008509
Purpose: To assess effects of α-blockers compared with standard therapy for ureteral stones 1 cm or smaller in adult patients presenting with symptoms of ureteral stone disease.
Methods: meta-analysis of 67 RCTs for ureteral stone passage in 10509 adult patients.
Results: Treatment with an α-blocker resulted in increased stone clearance (RR 1.45, 95% CI:1.36-1.55, low quality evidence). Subgroup analyses suggest that α-blockers may be less effective for smaller stones (≤5 mm).
Conclusions: α-blockers likely increase stone clearance, but also slightly increase the risk of major adverse events.

Main Elective Treatment Options
1. Conservative medical management
2. Extracorporeal SWL: less invasive (sedation only, no internal instrumentation), less successful
3. URS laser lithotripsy: slightly more invasive (usually GA or spinal, instrumentation required, usually outpatient), more successful
4. PCNL: more invasive (requires GA, involves puncture of kidney, often needs admission), most successful for larger stones
5. Laparoscopic or open surgery: rare in modern era unless performing other concomitant procedure (e.g. UPJ obstruction correction)

Prevention
- dietary modification
  - increase fluid (>2 L/d), citrate intake (lemon juice, orange juice)
  - reduce animal protein, oxalate, Na^+, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
- medications
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria

Tuberous Sclerosis
- Syndrome characterized by mental retardation, epilepsy, and adenoma sebaceum
- 45-80% of patients also present with angiomyolipomas, which are often multiple and bilateral

Table 13. Stone Classification

Type of Stone	Calcium (75-85%)	Uric Acid (5-10%)	Struvite (5-10%)	Cystine (1%)
Etiology	Hypercalciuria Hyperuricosuria (25% of patients with Ca^{2+}stones) Hyperoxaluria (<5% of patients) Hypocitraturia (12% of patients) Other causes: Hypomagnesemia – associated with hyperoxaluria and hypocitraturia High dietary Na^+ Decreased urinary proteins High urinary pH, low urine volume (e.g. GI water loss) Hyperparathyroidism, obesity, gout, DM	Uric acid precipitates in low volume, acidic urine with a high uric acid concentration: Hyperuricosuria alone Drugs (ASA, thiazides) Diet (purine-rich red meats) Hyperuricosuria with hyperuricemia Gout High rate of cell turnover or cell death (leukemia, cytotoxic drugs)	Infection with urea-splitting organisms (*Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)	Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in "COLA" in urine (cystine, ornithine, lysine, arginine)
Key Features	Radiopaque on KUB x-ray Reducing dietary $Ca^{2+}$is NOT an effective method of prevention/treatment	Radiolucent on KUB x-ray Radiopaque on CT Acidic urine, pH <5.5 (NOT necessarily elevated urinary uric acid)	Perpetuates UTI because the stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: *E. coli* infection does not cause struvite stones M:F=3:1, UTI more common in female	Aggressive stone disease seen in children and young adults Recurrent stone formation, FMHx Often staghorn calculi Faintly radiopaque on KUB x-ray Positive urine sodium nitroprusside test, urine chromatography for cystine
Treatment Medical if stone <5 mm and no complications Procedural/Surgical treatment if stone >5 mm or presence of complications Can observe selected, asymptomatic renal stones	Fluids to increase urine volume to >2 L/d For calcium stones: increase citrate in diet, reduce salt, moderate oxalate-rich foods, weight loss Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol Mixed calcium and struvite: ABx (stone must be removed to treat infection)	Increased fluid intake Alkalinization of urine to pH 6.5-7 (potassium citrate, sodium bicarbonate) ± allopurinol Be careful not be make urine too alkaline (pH >7), can result in calcium phosphate stones	Complete stone clearance ABx for 6 wk Regular follow-up urine cultures	Increased fluid intake (3-4 L of urine/d) Alkalinize urine (bicarbonate, potassium citrate), penicillamine/ α-mercaptopropionylglycine or Captopril (form complex with cystine) SWL not effective

Urological Neoplasms

Approach to Renal Mass

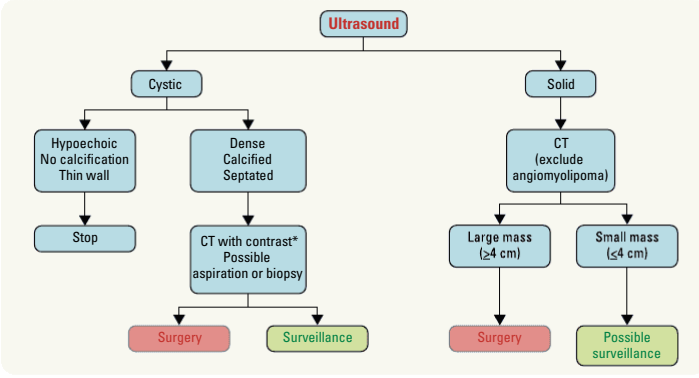


Figure 13. Workup of a renal mass
*Imaging modality may be different in cases of contrast allergy or elevated creatinine

There is controversy over optimal management of small renal masses

Percutaneous needle biopsies of cystic renal masses may lead to peritoneal seeding

Tuberous Sclerosis

Syndrome characterized by mental retardation, epilepsy, and adenoma sebaceum

45-80% of patients also present with angiomyolipomas, which are often multiple and bilateral

APPROACH TO SMALL SOLID RENAL MASSES

- initial workup: kidney function (Cr, eGFR), CXR, contrast CT or MRI, ± renal biopsy
- limited life expectancy: watchful waiting
- <2 cm: active surveillance with imaging q3-6 mo, proceed to intervention if growth >2 cm, or growth >0.5 cm/yr, or patient preference
- 2-4 cm: active surveillance or definitive therapy (biopsy + thermal ablation or partial nephrectomy, if feasible)

Benign Renal Neoplasms

CYSTIC KIDNEY DISEASE

- simple cysts: usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - Bosniak Classification is used to stratify for risk of malignancy based on cyst features from contrast CT
- PCKD
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure, adult-onset
- medullary sponge kidney: cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- von Hippel-Lindau syndrome: multiple bilateral cysts and/or renal cell carcinomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

Table 14. Bosniak Classification of Renal Cysts

Class	Features	Risk of Malignancy	Management Plan
I (simple cyst)	Round, no septa/calcifications/ enhancement, homogeneous, <20 HU	Near zero	No follow-up
II (simple cyst)	Thin septum (<1 mm), fine calcification, no enhancement, <3 cm, >20 HU	Minimal	No follow-up
IIF (minimally complex cyst)	Multiple thin septa, calcifications, no enhancement, >3 cm, >20 HU	5-20%	Follow-up, imaging q6-12 mo, surgical resection if lesion evolves
III (complex cyst)	Irregular, thickened, calcified septa with enhancement	>50% * growing literature suggesting might be lower	Surgical resection * growing literature suggesting surveillance might be safe
IV (likely malignant)	Irregular, thickened, calcified septa with enhancement, enhancing soft-tissue components	>90%	Surgical resection

Table 15. Benign Renal Masses

	Angiomyolipoma (Renal Hamartoma)	Renal Oncocytoma
Epidemiology	<10% of adult renal tumours F>M 20% associated with tuberous sclerosis (especially if multiple, recurrent)	3-7% of renal tumours M>F Oncocytomas also found in adrenal, thyroid, and parathyroid glands
Characteristics	Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma) May extend into regional lymphatics and other organs and become symptomatic	Spherical, capsulated with possible central scar Histologically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct
Diagnosis	Incidental finding on CT Negative attenuation (-20 HU) on CT is pathognomonic Rare presentation of hematuria, flank pain, and palpable mass (same as RCC)	Incidental finding on CT Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise Biopsy may be performed to rule out malignancy
Management	May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy) Potential role for mechanistic target of rapamycin (mTOR) inhibitors in unresectable/metastatic disease Follow with serial U/S	Surveillance for most Partial/radical nephrectomy for large masses

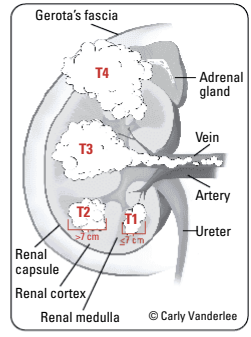


Figure 14. RCC staging

Malignant Renal Neoplasms

RENAL CELL CARCINOMA

Etiology
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome, hereditary papillary renal carcinoma, Birt Hogg Dubé syndrome, and hereditary leiomyomatosis and renal cell cancer

Epidemiology
- 85% of primary malignant tumours in kidney, ~3% of all malignancies
- M:F=1.5:1
- peak incidence at ages 50-60

Pathology
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobe (5-10%), collecting duct (<1%), other (<1%)
- sarcomatoid or rhabdoid elements in any subtype are markers of poor prognosis

Risk Factors
- top 3 risk factors: smoking, HTN, obesity
- end-stage renal disease (acquired renal cystic disease)
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

Clinical Features
- usually asymptomatic: frequently diagnosed incidentally by U/S or CT (>50%)
- indicators for poor prognosis: weight loss, weakness, anemia, bone pain
- classic "too late triad" found in 10-15%
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- metastases: seen in a 1/3 of new cases; additional 20-40% will go on to develop metastases (mostly in late presentations or large tumours)
  - most common sites: bone, brain, lung, and liver
  - may invade renal veins and inferior vena cava (IVC) lumen
  - this may result in ascites, hepatic dysfunction, right atrial tumour, varicocele, and pulmonary emboli

Investigations
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A
- renal U/S: solid vs. cystic lesion
- contrast-enhanced CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
- MRI: useful for evaluation of complex cystic lesions indeterminate on CT; good way to assess IVC thrombus
- renal biopsy: to confirm diagnosis, if considering observation or other non-surgical ablative therapy
- genetic testing: consider if FHx of von Hippel-Lindau syndrome, non-clear cell carcinoma, bilateral/multifocal tumour, onset ≤45 yr, FHx of renal tumour, or any renal tumour with Hx of pneumothorax, dermatologic findings, associated tumours, lymphangiomyomatosis, or childhood seizure disorder

Role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

RCC Systemic Effects: Paraneoplastic Syndromes (10-40% of Patients)

Hematopoietic disturbances: anemia, polycythemia, raised Erythrocyte Sedimentation Rate (ESR)

Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)

Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour

Hemodynamic alterations: systolic HTN (due to arteriovenous shunting), peripheral edema (due to caval obstruction)

Staging
- involves abdo/pelvis CT, CXR, liver enzymes and LFTs, bone/head imaging (if symptoms dictate)

Table 16. 2018 TNM Classification of Renal Cell Carcinoma (AJCC 8th edition)

T	N	M
TX: primary tumour cannot be assessed	**NX**: regional lymph nodes cannot be assessed	**cM0**: no evidence of distant metastasis
T1: tumour <7 cm, confined to renal parenchyma **T1a**: <4 cm **T1b**: 4-7 cm	**N0**: no regional lymph node metastasis **N1**: metastasis in regional lymph nodes	**cM1**: presence of distant metastasis **pM1**: presence of distant metastasis, microscopically confirmed
T2: tumour >7 cm, confined to renal parenchyma **T2a**: >7 cm but ≤10 cm **T2b**: >10 cm	**N Suffix** **(sn)**: regional lymph node metastasis identified by SLN biopsy only **(f)**: regional lymph node metastasis identified by FNA or core needle biopsy only	
T3: tumour extends into major veins or perinephric tissues, but NOT into ipsilateral adrenal or beyond Gerota's fascia **T3a**: into renal vein or sinus fat **T3b**: into infradiaphragmatic IVC **T3c**: into supradiaphragmatic IVC		
T4: tumour extends beyond Gerota's fascia including extension into ipsilateral adrenal		
T Suffix **(m)**: if synchronous primary tumours are found in single organ		

Treatment
- surgical (open, laparoscopic, robotic)
  - radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota's capsule
  - partial nephrectomy (nephron-sparing): small tumour (roughly <4 cm) or solitary kidney/ bilateral tumours
  - surgical removal of solitary metastasis may be considered
- ablative techniques (percutaneous or lap-assisted)
  - radiofrequency ablation (RFA)
  - cryoablation
  - palliative radiation to painful bony lesions
- radiation therapy (SBRT)
  - for non-surgical candidates
- therapy for advanced stage
  - new immunologic inhibitors (e.g. pembrolizumab, ipilimumab, nivolumab)
  - tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)
  - IFNα: monotherapy has been largely replaced by molecularly targeted agents listed above

Prognosis
- stage at diagnosis most important prognostic factor
  - T1: 90-100% 5 yr survival
  - T2-T3: 60% 5 yr survival
  - metastatic disease: <5% 10 yr survival
- predictors of relapse: tumour grade, local extent of the primary tumour, presence of local metastases, histological subtype

Carcinoma of the Renal Pelvis and Ureter

Etiology
- risk factors include:
  - smoking
  - dietary/chemical exposures (aristolochic acid, industrial dyes and solvents: aniline dyes)
  - analgesic misuse (acetaminophen, ASA, and phenacetin)
  - Balkan nephropathy
  - prior exposure to cyclophosphamide

Epidemiology
- rare: accounts for 5% of all UC
- frequently multifocal, 2-5% are bilateral
- M:F=3:1
- relative incidence: bladder:renal:ureter=100:10:1
- consider Lynch syndrome if PMHx for other malignancies (e.g. colorectal, stomach, prostate, endometrial, etc.)

Pathology
- 85% are UC; others include SCC and adenocarcinoma
- UC of ureter and renal pelvis are histologically similar to bladder UC

Clinical Features
- gross/microscopic hematuria
- flank pain
- storage or voiding symptoms (dysuria only if lower urinary tract involved)
- flank mass ± hydronephrosis (10-20%)

Investigations
- CTU
- cystoscopy and retrograde pyelogram

Treatment
- radical nephroureterectomy with excision of ipsilateral bladder cuff
- distal ureterectomy for distal ureteral tumours with concomitant ureteral reimplant
- segmental resection with uretero-ureterostomy for some mid-ureteral tumours is also done
- adjuvant chemotherapy (gemcitabine-platinum)
- emerging role for endoscopic laser ablation in patients with low grade disease, poor baseline renal health

Bladder Carcinoma

Etiology
- unknown, but environmental risk factors include:
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior Hx of radiation treatment to the pelvis
  - *Schistosoma hematobium* infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)
  - aristolochic acid: associated with Balkan nephropathy (renal failure, upper tract UC) and Chinese herbal nephropathy

Epidemiology
- 2nd most common urological malignancy
- M:F=3:1, more common among whites than blacks
- mean age at diagnosis is 65 yr

Pathology
- classification
  - UC >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of UC at diagnosis
  - non-muscle invasive (75%) → >80% overall survival
    - 15% of these will progress to invasive UC
    - majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5 yr survival
    - 85% have no prior history of superficial UC (i.e. *de novo*)
    - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma *in situ* (CIS)→ flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis, higher recurrence rates following radical cystectomy, associated with radioresistance
  - usually multifocal
  - may progress to invasive UC

Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumour (e.g. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider CIS
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (N/V and diarrhea); bad prognostic factor; likely muscle invasive

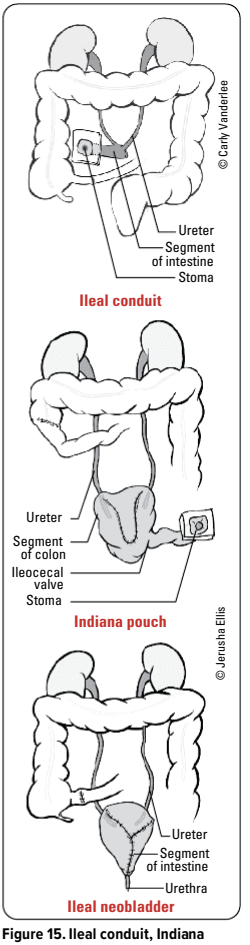


Figure 15. Ileal conduit, Indiana pouch, ileal neobladder

Differential Diagnosis of Filling Defect in Urinary Tract

Urothelial carcinoma (differentiate via cytology and CT scan)

Uric acid stone (differentiate via cytology and CT scan)

Blood clot

Pyelitis cystica

Papillary necrosis

Fungus ball

Gas bubble from gas producing organisms

Investigations

- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast → look for filling defects in upper tracts and metastases
- cystoscopy with biopsy (if small lesion)
- TURBT (gold standard, diagnostic, and often therapeutic) → establish diagnosis and determine depth of penetration
  - involvement of muscularis propria confirms muscle invasion (T2)
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP); utility in clinical practice debatable

Grading

- low grade: ≤10% invasive, 60% recur locally
- high grade: 50-80% are invasive or are expected to progress to invasive over time

Staging

- for invasive disease: examination under anesthesia following TURBT, CT, or MRI of abdomen and pelvis, CT or MR urography, CT chest or CXR, bone scan in setting of bony pain/hypercalcemia/elevated ALP (metastatic workup)

Table 17. 2018 TNM Classification of Bladder Carcinoma (AJCC 8th edition)

T	N	M
TX: primary tumour cannot be assessed **T0**: no evidence of primary tumour **Ta**: noninvasive papillary carcinoma **Tis**: CIS: "flat tumour" **T1**: tumour invades subepithelial connective tissue **T2**: tumour invades muscularis propria **pT2a**: tumour invades superficial muscularis propria (inner half) **pT2b**: tumour invades deep muscularis propria (outer half) **T3**: tumour invades perivesical tissue **pT3a**: microscopically **pT3b**: macroscopically (extravesical mass) **T4**: tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall **T4a**: tumour invades prostatic stroma, uterus, vagina **T4b**: tumour invades pelvic wall, abdominal wall **T Suffix** **(m)**: synchronous primary tumours are found in single organ	**NX**: lymph nodes cannot be assessed **N0**: no lymph node metastasis **N1**: single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node) **N2**: multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis) **N3**: lymph node metastasis to the common iliac lymph nodes **N Suffix** **(sn)**: regional lymph node metastasis identified by SLN biopsy only **(f)**: regional lymph node metastasis identified by FNA or core needle biopsy only	**cM0**: no distant metastasis **cM1**: distant metastasis **cM1a**: distant metastasis limited to lymph nodes beyond the common iliacs **cM1b**: non-lymph-node distant metastasis **pM1**: distant metastasis, microscopically confirmed **pM1a**: distant metastasis limited to lymph nodes beyond the common iliacs, microscopically confirmed **pM1b**: non-lymph-node distant metastasis microscopically confirmed

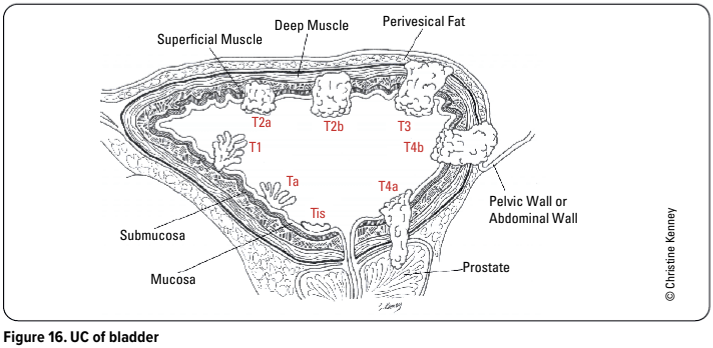


Figure 16. UC of bladder

The "field defect" theory helps to explain why UC has multiple lesions and has a high recurrence rate. The entire urothelium (pelvis to bladder) is bathed in carcinogens

The ENTIRE urinary tract must be evaluated in patients with hematuria unless there is clear evidence of glomerular bleeding (e.g. red cell casts, dysmorphic RBCs, etc.)

Cystoscopy is the initial procedure of choice for the diagnosis and staging of urothelial malignancy

Unexplained hematuria in any individual >40 y/o must be investigated to rule out a malignancy

Tumour grade is the single most important prognostic factor for progression

See Landmark Urology Trials table for more information on neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for improved outcomes in patients with locally advanced bladder cancer.

NMIBC and BCG
AHRQ Publication 2015:15-EHC017-EF #153
Summary: BCG is the only intravesical therapy associated with decreased risk of bladder cancer progression; however, it is also associated with a high rate of adverse events. More research is needed to define optimal dose/regimen.
Methods: Review of Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of SR, Health Technology Assessment, National Health Sciences Economic Evaluation, Database of Abstract of Review of Effects for studies on NMIBC interventions, including intravesical therapy.
Results: BCG is superior in prevention of bladder cancer recurrence compared to no intravesical therapy. BCG is superior to doxorubicin, epirubicin, and mitomycin in prevention of bladder cancer recurrence.

Treatment

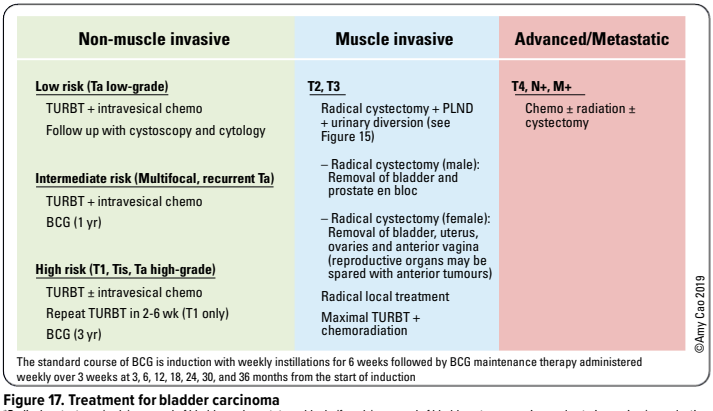

Non-muscle invasive
Muscle invasive
Advanced/Metastatic
Low risk (Ta low-grade)
TURBT + intravesical chemo
Follow up with cystoscopy and cytology
Intermediate risk (Multifocal, recurrent Ta)
TURBT + intravesical chemo
BCG (1 yr)
High risk (T1, Tis, Ta high-grade)
TURBT ± intravesical chemo
Repeat TURBT in 2-6 wk (T1 only)
BCG (3 yr)
T2, T3
Radical cystectomy + PLND + urinary diversion (see Figure 15)
– Radical cystectomy (male): Removal of bladder and prostate en bloc
– Radical cystectomy (female): Removal of bladder, uterus, ovaries and anterior vagina (reproductive organs may be spared with anterior tumours)
Radical local treatment
Maximal TURBT + chemoradiation
T4, N+, M+
Chemo ± radiation ± cystectomy
©Amy Cao 2019
The standard course of BCG is induction with weekly instillations for 6 weeks followed by BCG maintenance therapy administered weekly over 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months from the start of induction

Figure 17. Treatment for bladder carcinoma
*Radical cystectomy (male): removal of bladder and prostate en block, (female): removal of bladder, uterus, ovaries, and anterior vagina (reproductive organs may be spared with anterior tumours)

The standard course of BCG is induction with weekly instillations for 6 wk followed by BCG maintenance therapy administered weekly over 3 wk at 3, 6, 12, 18, 24, 30, and 36 mo from the start of induction.

Prognosis
- depends on stage, grade, size, number of lesions, recurrence, and presence of CIS
  - T1: 90% 5 yr survival
  - T2: 55% 5 yr survival
  - T3: 30% 5 yr survival
  - T4/N+/M+: <5% 5 yr survival

Prostate Cancer

Etiology
- not known
- risk factors
  - age >50 yr, risk increases 1% per yr after 65 yr
  - increased incidence in persons of African descent
  - high dietary fat (2x)
  - FMHx
    - 1st degree relative (2x)
    - 1st and 2nd degree relatives (9x)
  - positive BRCA (BReast CAncer gene) mutation

Epidemiology
- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between ages 60 and 85; mean age at diagnosis is 65

Pathology
- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma of the prostate (4.5%)
  - associated with UC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle
  - other: squamous cell, small cell

Anatomy
- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

Clinical Features
- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see *PSA Screening, U28*

- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
- metastatic disease
  - bony metastases to axial skeleton common
  - visceral metastases are less common (liver, lung, and adrenal gland most common sites)
  - leg pain and edema with nodal metastases obstructing lymphatic and venous drainage

Methods of Spread
- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

Investigations
- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan (only if bone pain, high-risk disease, Gleason score >7, or PSA >20 ng/mL)
- CT scan to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsy, and active surveillance

Early Detection of Prostate Cancer: American Urological Association Guidelines
J Urol 2013;190: 419
1. For men aged 55 to 69 yr who are considering PSA screening, it is strongly recommended to proceed based on values and preferences following shared decision-making.
2. Routine PSA screening in men between ages 40 to 54 yr at average risk is NOT recommended .
3. Routine PSA screening in men age 70+ yr or any man with less than a 10 to 15 yr life expectancy is NOT recommended.

Table 18. 2018 TNM Classification of Prostate Carcinoma (AJCC 8th edition)

T	N	M
TX: primary tumour cannot be assessed	**NX**: regional lymph nodes were not assessed	**M0**: no distant metastasis
T0: no evidence of primary tumour	**N0**: no regional lymph node metastasis	**cM1**: distant metastasis **cM1a**: non-regional lymph nodes **cM1b**: bone(s) **cM1c**: other site(s) with or without bone disease
T1: clinically undetectable tumour, normal DRE and TRUS **T1a**: tumour incidental histologic finding in <5% of tissue resected **T1b**: tumour incidental histologic finding in >5% of tissue resected **T1c**: tumour identified by needle biopsy (due to elevated PSA level)	**N1**: spread to regional lymph nodes **N Suffix** **(sn):** regional lymph node metastasis identified by SLN biopsy only **(f):** regional lymph node metastasis identified by FNA or core needle biopsy only	**pM1**: distant metastasis, microscopically confirmed **pM1a**: non-regional lymph nodes, microscopically confirmed **pM1b**: bone(s) microscopically confirmed **pM1c**: other site(s) with or without bone disease, microscopically confirmed
T2: palpable, confined to prostate **T2a**: tumour involving ≤ one half of one lobe **T2b**: tumour involving > one half of one lobe, but not both lobes **T2c**: tumour involving both lobes		
T3: tumour extends through prostate capsule **T3a**: extracapsular extension (unilateral or bilateral) **T3b**: tumour invading seminal vesicle(s)		
T4: tumour invades adjacent structures (besides seminal vesicles)		
T Prefix **(c)**: clinical T **(p)**: pathological T. There is no pathological T1		
T Suffix **(m)**: synchronous primary tumours are found in single organ		

Table 19. Prostate Cancer Mortality Risk

	Low-Risk (if any of following)	Intermediate-Risk (if any of following)	High-Risk (if any of following)
PSA	<10	10-20	>20
Gleason Score	<7 (Grade Group 1)	7 (Grade Group 2 and 3)	8-10 (Grade Group 4 and 5)
Stage	pT1-2a	pT2b-T2c	pT3/4

See Landmark Urology Trials table for more information on 10-yr outcomes for patients with localized prostate cancer after monitoring, surgery, or radiotherapy.

Treatment
- T1/T2 (localized, low-risk)
  - if adequate life expectancy or no other significant comorbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - active surveillance for low-risk, small volume Gleason score <7 prostate cancer shown to be safe for most
  - minimal differences in cure or recurrence rates between definitive treatment modalities
  - in older population: watchful waiting and palliative treatment for symptomatic progression
  - alternative treatment options include: HIFU, cryoablation, focal laser ablation

- T1/T2 (intermediate or high-risk)
  - definitive therapy over active surveillance
  - watchful waiting in elderly or infirm
- T3, T4
  - ADT (with calcium, vitamin D, bisphosphonates) + EBRT/docetaxel/abiraterone
  - enzalutamide, apalutamide, abiraterone if locally advanced
  - radiation therapy for oligometastatic disease (case-by-case basis)
- N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bilateral orchiectomy – decreases testosterone production by 90%
  - GnRH agonists (e.g. leuprolide, goserelin), see *Table 28, U47*, GnRH antagonist (e.g. degarelix) with one of enzalutamide, apalutamide, darolutamide + docetaxel, abiraterone, docetaxel alone
  - antiandrogens (e.g. bicalutamide)
  - local irradiation of painful secondaries or half-body irradiation
- CRPC
  - ADT should be maintained
  - non-metastatic CRPC: observation vs. apalutamide, enzalutamide, or darolutamide
  - metastatic CRPC: abiraterone, enzalutamide, docetaxel-based chemotherapy
    - post-docetaxel: second-line chemotherapy cabazitaxel
    - if symptomatic without visceral metastases: radium-223
    - Homologous Recombination Repair (HRR) mutation: olaparib
    - bone metastases: denosumab and/or zoledronic acid is recommended ± palliative radiation
    - Lutetium-177 post docetaxel and ARPI (enzalutamide/abiraterone)

Table 20. Treatment Options for Localized Prostate Cancer

Modality	Population Considered	Limitations
Watchful Waiting	Short life expectancy (<5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses	Disease progression
Active Surveillance (serial PSA, DRE, and biopsies)	Low grade disease, good follow-up; is still considering more curative treatment if disease progresses	Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date
Brachytherapy	Low volume, low PSA (<10), low grade	ED (50%), long-term effectiveness not well-established
EBRT	Locally advanced disease, older patients	Radiation proctitis (5%), ED (25-50%), risk of rectal and bladder cancer
RP	Young patients (<75 yr), high-risk disease	Incontinence (10%), ED (30-50%)

*Other options include cryosurgery, HIFU, hormonal ablation

Prognosis
- T1-T2: comparable to normal life expectancy
- T3-T4: 40-70% 10 yr survival
- N +and/or M +: 4% 5 yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

PSA Screening

Digital Rectal Exam
- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

Prostate Specific Antigen
- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in setting of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cut-off point
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- decreased free:total PSA, elevated PSA velocity and elevated PSA density associated with increased CaP rates

Causes of Increased PSA
BPH, prostatitis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy

PSA is specific to the PROSTATE, but NOT to prostate cancer

Screening Recommendations

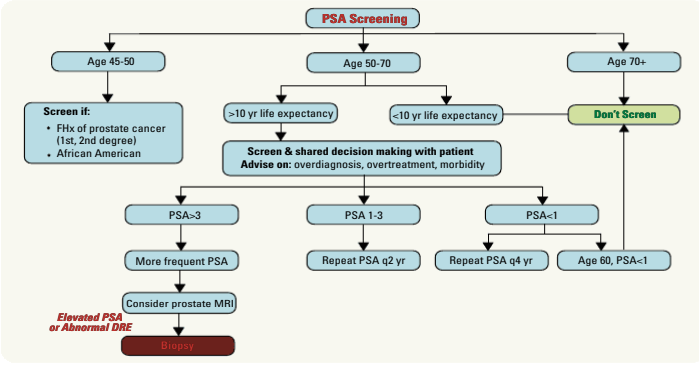


Figure 18. Canadian Urological Association guidelines on PSA screening (2017)

Long-Term Follow-Up on PSA Screening
Lancet 2014;384:2027-2035
Summary: At 13 yr follow-up, PSA screening is favourable, showing a significant 21% relative prostate cancer mortality reduction. The number needed to screen and to treat from this trial were lower than those observed in breast cancer trials. However, the risks associated with screening need to be considered when considering population-level screening programs.
Methods: Multi-centre RCT with predefined central database, analysis, and core age group (55-69 yr) evaluating PSA in 8 European countries. Incidence and mortality truncated at 9, 11, and 13 yr follow-up in the intervention arm was compared to control arm.
Results: RR of PCa incidence between intervention and control arms was 1.91 after 9 yr follow-up, 1.66 at 11 yr follow-up, and 1.67 at 13 yr follow-up. RR of PCa mortality was 0.85, 0.78, and 0.79, at 9, 11, 13 yr follow-up, respectively. At 13 yr follow-up in PSA screening group, relative RR is 21%, and absolute RR from death is 1.28 per 1000 men.

Testicular Tumours

Etiology/Risk Factors
- cryptorchidism, atrophy, sex hormones, HIV infection, infertility, FMHx, PMHx of testicular cancer

Epidemiology
- rare, but most common solid malignancy in young males 15-35 yr
- any solid testicular mass or acute hydrocoele in young patient – must rule out malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously/synchronous or successively/metachronous)

Pathology
- primary
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumours (all are malignant)
    - seminoma (35%) → classic, anaplastic, spermatocytic
    - NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<<1%), mixed cell type (40%)
  - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

Clinical Features
- painless testicular enlargement (painful if intratesticular hemorrhage or infarction)
- dull, heavy ache in lower abdomen, anal area, or scrotum
- associated hydrocele (10%)
- coincidental trauma (10%)
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumour effects
- supraclavicular and inguinal lymphadenopathy
- abdominal mass (retroperitoneal lymph node metastases)

Methods of Spread
- local spread follows lymphatics
  - right → medial, paracaval, anterior, and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - "cross-over" metastases from right to left are fairly common, but no reports from left to right
- hematogenous most commonly to lung, liver, bones, and kidney

Investigations

- diagnosis is established by pathological evaluation of specimen obtained by radical inguinal orchiectomy
- tumour markers (β-hCG, LDH, AFP)
  - β-hCG and AFP are positive in 85% of non-seminomatous tumours
  - elevated marker levels return to normal postoperatively if no metastasis
  - β-hCG positive in 7% of pure seminomas, AFP never elevated with seminoma
- testicular U/S (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
- evidence of testicular microlithiasis is not a risk factor for testicular cancer
- needle aspiration contraindicated

Testes and scrotum have different lymphatic drainage, therefore trans-scrotal approach for biopsy or orchiectomy should be avoided

Staging

- clinical: CXR (lung metastases), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)
  - stage I: disease limited to testis, epididymis, or spermatic cord
  - stage II: disease limited to the retroperitoneal nodes
  - stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

Table 21. 2018 TNM Classification of Testicular Carcinoma (AJCC 8th edition)

T	N	M
TX: primary tumour cannot be assessed **T0**: no evidence of primary tumour **Tis**: intratubular germ cell neoplasia **T1**: limited to testis and epididymis without lymphovascular invasion **T1a**: tumour <3 cm **T1b**: tumour >3 cm **T2**: limited to testis and epididymis with lymphovascular invasion or invading hilar soft tissue or epididymis, or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion **T3**: invasion of the spermatic cord ± lymphovascular invasion **T4**: invasion of the scrotum ± invasion **T Prefix** **(c)**: clinical T. except for Tis confirmed by biopsy an T4, the extent of primary tumour is classified by radical orchiectomy **(p)**: pathological T. subclassification of pT1 applies only to pure seminoma **T Suffix** **(m):** synchronous primary tumours are found in single organ	**NX**: regional lymph nodes were not assessed **N0**: no regional lymph node metastasis **N1**: metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension **N2**: metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension **N3**: metastasis with a lymph node mass more than 5 cm in greatest dimension **N Prefix** **(c)**: clinical N **(p)**: pathological N **N Suffix** **(sn)**: regional lymph node metastasis identified by SLN biopsy only **(f)**: regional lymph node metastasis identified by FNA or core needle biopsy only	**M0**: no distant metastases **cM1**: distant metastases **cM1a**: non-retroperitoneal nodal or pulmonary metastases **cM1b**: non-pulmonary visceral metastases **pM1**: distant metastases, microscopically confirmed **pM1a**: non-retroperitoneal nodal or pulmonary metastases, microscopically confirmed **pM1b**: non-pulmonary visceral metastases, microscopically confirmed

Management

- radical orchiectomy through inguinal incision for all stages – ligate spermatic cord inside inguinal canal
- consider sperm banking, testicular prosthesis
- adjuvant therapies (see *Figure 19, U31*)

Orchiopexy
Surgical descent (orchiopexy) of undescended testis does not eliminate the risk of malignancy, but allows for earlier detection by self-examination and reduces the risk of infertility

Prognosis

- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

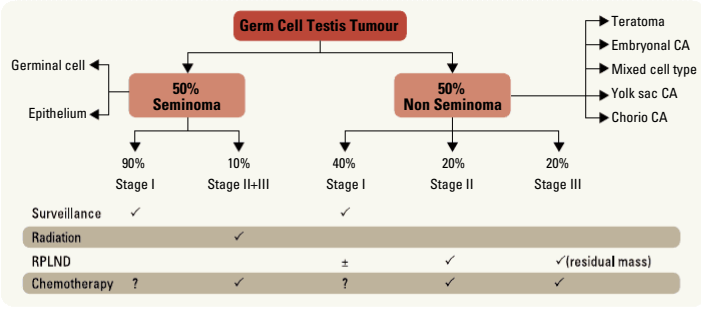


Figure 19. Adjuvant management of testicular cancer post-orchiectomy
Adapted from Dr. MAS Jewett

Layers of the Scrotum

SDECITT
Skin
Dartos muscle and fascia
External spermatic fascia
Cremasteric fascia
Internal spermatic fascia
Tunica vaginalis
Tunica albuginea

Penile Tumours

Epidemiology
- rare (<1% of cancer in males in U.S.)
- most common in ages 50-59

Benign
- cyst, hemangioma, nevus, papilloma

Pre-Malignant
- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

Pre-invasive Cancer
- carcinoma *in situ*
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil, topical imiquimod

Malignant
- risk factors
  - chronic inflammatory disease
  - STI
  - phimosis
  - uncircumcised penis
- 2% of all urogenital cancers
- SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion
- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

Treatment
- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
- consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.), if available

Scrotal Masses

Table 22. Differentiating between Scrotal Masses

Condition	Pain	Palpation	Additional Findings
Torsion	+	Diffuse tenderness Horizontal lie of testicle	Absent cremaster reflex, negative Prehn's sign
Epididymitis	+	Epididymal tenderness	Present cremaster reflex, positive Prehn's sign
Orchitis	+	Diffuse tenderness	Present cremaster reflex, positive Prehn's sign
Hematocele	+	Diffuse tenderness	No transillumination
Hydrocele	–	Testis not separable from hydrocele, cord palpable	Transillumination, Hx of trauma
Spermatocele	–	Testis separable from spermatocele, cord palpable	Transillumination
Varicocele	–	Bag of worms	No transillumination, increases in size with valsalva, decrease in size if supine
Indirect Inguinal	– (+ if strangulated)	Testis separable from hernia, cord not palpable, cough impulse may transmit, may be reducible	No transillumination
Tumour	– (+ if hemorrhagic)	Hard lump/nodule	
Generalized/Dependent Edema	–	Diffuse swelling	Often postoperative or immobilized, check for liver dysfunction
Idiopathic	–		

Varicocele Grading
Grade 1: palpable only with Valsalva manoeuvre
Grade 2: palpable without Valsalva
Grade 3: visible through scrotal skin

Indications for Treatment of Varicocele

Impaired sperm quality or quantity

Pain or dull ache affecting QOL

Affected testis fails to grow in adolescents

Cosmetic indications (especially in adolescents)

Table 23. Benign Scrotal Masses

Type	Varicocele	Spermatocele	Hydrocele	Testicular Torsion	Inguinal Hernia
Definition	Dilatation and tortuosity of pampiniform plexus	A benign, sperm-filled epididymal retention cyst	Collection of serous fluid that results from a defect or irritation in the tunica vaginalis	Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction	Protrusion of abdominal contents through the inguinal canal into the scrotum
Etiology	15% of men Due to incompetent valves in the testicular veins 90% left-sided	Multiple theories, including: Distal obstruction Aneurysmal dilations of the epididymis Agglutinated germ cells	Usually idiopathic Found in 5-10% testicular tumours Associated with trauma/infection Communicating: patent processus vaginalis, changes size during day (pediatric) Non-communicating: non-patent processus vaginalis (adult)	Trauma Cryptorchidism "Bell clapper deformity" Many occur in sleep (50%) Necrosis of glands in 5-6 h	Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness
Hx/P/E	"Bag of worms" Often painless Pulsates with Valsalva	Non-tender, cystic mass Transilluminates	Non-tender, intrascrotal mass Cystic Transilluminates	Acute onset severe scrotal pain, swelling GI upsets cases Retracted and transverse testicle (horizontal lie) Negative Phren's sign Absent cremasteric reflex	A small bulge in the groin that may increase in size with Valsalva and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising
Investigations	P/E Valsava	P/E U/S to rule out tumour	U/S to rule out tumour	U/S Doppler with probe over testicular artery Decrease uptake on 99mTc-pertechnetate scintillation scan (doughnut sign)	Hx and P/E Invagination of the scrotum Valsalva
Treatment	Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (coils) Repair may improve sperm count/motility	Conservative Excise if symptomatic	Conservative Needle drainage (high rate of surgical recurrence) Surgical	Emergency surgical exploration and bilateral orchiopexy Definitive diagnosis NOT necessary to take to OR Orchiectomy if absent restoration of flow to testicle	Surgical repair

TORSION OF TESTICULAR APPENDIX

- twisting of testicular/epididymal vestigial appendix

Signs and Symptoms

- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
- "blue dot sign"
  - blue infarcted appendage seen through scrotal skin in children (can usually be palpated as small, tender lump)

Indications for Treatment of Varicocele

Impaired sperm quality or quantity

Pain or dull ache affecting QOL

Affected testis fails to grow in adolescents

Cosmetic indications (especially in adolescents)

Treatment
- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

HEMATOCELE
- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

Treatment
- ice packs, analgesics, surgical drainage, and hydrocele repair

Acute scrotal swelling/pain in young boys is torsion until proven otherwise

Transillumination refers to light being transmitted through tissue (i.e. due to excess fluid)

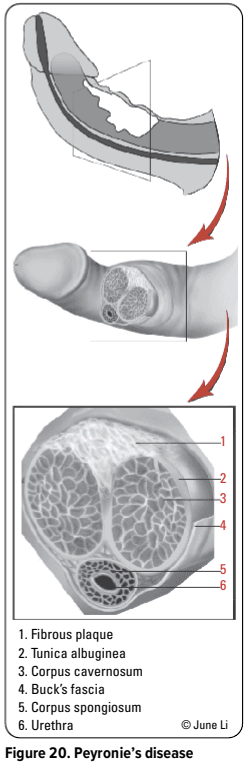
Differential of a Benign Scrotal Mass

HIS BITS
Hydrocele
Infection (epididymitis/orchitis)
Sperm (spermatocele)
Blood (hematocele)
Intestines (hernia)
Torsion
Some veins (varicocele)

Penile Complaints

Table 24. Penile Complaints

Type	Peyronie's Disease	Priapism	Paraphimosis	Phimosis	Premature Ejaculation
Definition	Acquired curvature of penile shaft secondary to fibrous thickening of tunica albuginea	Prolonged erection lasting >4 h in the absence of sexual excitement/desire	Retracted foreskin (behind glans penis) that cannot be reduced	Inability to retract foreskin over glans penis	Ejaculation prior to when one or both partners desire it, either before or soon after intimacy
Etiology	Etiology unknown Trauma/repeated inflammation Familial predisposition Associated with DM, vascular disease, autoimmunity, Dupuytren's contracture, erectile dysfunction, urethral instrumentation	50% idiopathic **Ischemic (common):** Thromboembolic (sickle cell) Non-Ischemic: Trauma Medications Neurogenic	Iatrogenic (post cleaning/ instrumentation) Trauma Infectious (balanitis, balanoposthitis), sexual activity	Congenital (90% natural separation by age 3) Balanitis Poor hygiene	Psychological factors Primary: no period of acceptable control Secondary: symptoms after a period of control, not associated with general medical condition
Hx/P/E	Penile curvature/ shortening Pain with erection Poor erection distal to plaque	Painful erection ± signs of necrosis Note: non-ischemic (*high flow*) priapism may present without pain	Painful, swollen glans penis, foreskin Constricting band proximal to corona Dysuria, decreased urinary stream in children	Limitation and pain when attempting to retract foreskin Balanoposthitis (infection of prepuce)	Ejaculatory latency ≥1 min Inability to control or delay ejaculation Psychological distress
Investigations	Hx and P/E	Hx and P/E Cavernosal blood gas analysis Doppler U/S of the penis	Hx and P/E	Hx and P/E	Hx and P/E Testosterone levels if in conjunction with impotence
Treatment	**Supportive measures:** PDE5 inhibitor for ED NSAID for pain **Medical management:** Traction device Intralesional verapamil Intralesional collagenase **Surgical management:** Incision/excision of plaque Plication surgery Penile prosthesis	Treat reversible causes **High-flow:** Self-limited Consider arterial embolization **Low-flow:** Needle aspirated decompression Phenylephrine intracorporeal injection q3-5 min Surgical shunt no response within 1 h	Manual pressure (with analgesia) Dorsal slit Circumcision (urgent or elective to prevent recurrence)	Proper hygiene Topical corticosteroids Dorsal slit Circumcision	Rule out medical condition Address psychiatric concerns, counselling Medication: SSRI or clomipramine Topical lidocaine-prilocaine



1. Fibrous plaque
2. Tunica albuginea
3. Corpus cavernosum
4. Buck's fascia
5. Corpus spongiosum
6. Urethra

© June Li

Figure 20. Peyronie's disease

Erectile Dysfunction

Definition
- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

Physiology
- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic (dorsal penile/pudendal nerves (S2-4))

- erection ("POINT")
  - parasympathetics → NO release → increased cGMP within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
- emission ("SHOOT")
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
- ejaculation ("SHOOT")
  - bladder neck closure (sympathetic)
  - spasmodic contraction of bulbocavernosus and pelvic floor musculature (somatic)
- detumescence
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

Erections POINT AND SHOOT
parasympathetics = **point**
sympathetics/somatics = **shoot**

Classification

Table 25. Classification of Erectile Dysfunction

	Psychogenic*	Organic*
Prevalence	Less common	More common
Onset	Sudden	Gradual
Frequency	Sporadic	All circumstances
Variation	With partner and circumstance	No
Age	Younger	Older
Organic Risk Factors (HTN, DM, dyslipidemia)	No organic risk factors	Risk factors present
Nocturnal/Morning Erection	Present	Absent

*Combination can co-exist

Etiology ("IMPOTENCE")
Iatrogenic: pelvic surgery, pelvic radiation
Mechanical: Peyronie's, post-priapism
Psychological: depression, stress, anxiety, PTSD, widower syndrome
Occlusive: arterial HTN, DM, smoking, hyperlipidemia, PVD, impaired veno-occlusion
Trauma: penile/pelvic, bicycling
Extra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
Neurogenic: CNS (e.g. Parkinson's, MS, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
Chemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anticholinergics, antihistamines, antiandrogens (including 5-α reductase inhibitors), statins, GnRH agonists, illicit drugs
Endocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

Diagnosis

- complete Hx (include sexual, medical, and psychosocial aspects)
- self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale, erection hardness scale)
- focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
- lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
- specialized testing including nocturnal penile tumescence monitoring usually unnecessary
- evaluation of penile vasculature only relevant with past history of trauma (e.g. pelvic fracture)

Testosterone deficiency is an uncommon cause of ED

Treatment

- can often be managed by family physician, see sidebar for when to refer
- consider early sexual counselling referral
- must fully inform patient/partner of options, benefits and complications
- non-invasive
  - lifestyle changes (alcohol, smoking, physical activity), psychological (sexual counselling and education)
  - change precipitating medications
  - treat underlying causes (DM, CVD, HTN, endocrinopathies)
- minimally invasive
  - oral medication (see *Common Medications, U47*)
    - sildenafil, tadalafil, vardenafil, avanafil (not available in Canada): inhibits PDE5 to increase intracavernosal cGMP levels
      - all four have similar effectiveness, difference in onset of action is not clinically significant
      - tadalafil has longer half-life, no cyanopsia, and can be taken on empty or full stomach
      - tadalafil should be taken when needed instead of a set daily dose
  - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis
  - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra
  - insufficient evidence supporting low-intensity shockwave therapy
  - in patients with hypogonal testosterone, treat with dual testosterone and PDE5 inhibitor
- invasive
  - intracavernous vasodilator injection/self-injection
  - triple therapy (papaverine, phentolamine, PGE1), bimix (papaverine and phentolamine) or PGE1 alone
  - complications: priapism (overdose), fibrosis of tunica albuginea at site of repeated injections (Peyronie's plaque), and injection site injuries (pain, hematoma, etc.)
- surgical
  - penile implant (last resort): malleable or inflatable

PDE5 inhibitors are contraindicated in patients on nitrates/nitroglycerin due to severe hypotension

Initial trial of MUSE® or intracavernosal injection should be done under medical supervision

Penile vascular abnormalities may be a marker of risk for CV disease. Young men with vascular ED have 50x higher risk of having a CV event

Trauma

- see Emergency Medicine, ER7

Renal Trauma

Classification According to Severity
- minor
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

Etiology
- 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

Clinical Features
- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

Investigations
- labs
  - U/A: hematuria requires workup but degree does not correlate with the severity of injury
  - standard trauma labs (CBC and comprehensive metabolic panel)
- imaging
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

Staging (does not necessarily correlate well with clinical status)
- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: laceration causing urinary extravasation and/or main arterial or vein injury with contained hematoma
- V: shattered kidney or avulsion of pedicle

Treatment
- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization (majority now managed conservatively, nonoperatively)
  - absolute indications
    - hemorrhage and hemodynamic instability
  - relative indications
    - non-viable tissue and major laceration
    - urinary extravasation
    - vascular injury
    - expanding or pulsating perirenal mass
    - laparotomy for associated injury
- follow-up with U/S or CT before discharge, and at 6 wk

Complications
- HTN in 5% of renal trauma

Bladder Trauma

Classification
- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

Etiology
- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

Clinical Features
- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

Investigations
- U/A: gross hematuria in 90% of cases
- imaging (including CT cystogram and post-drainage films for extravasation)

Treatment
- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak, and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications
- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

Urethral Injuries

Etiology
- posterior urethra
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra
  - straddle injury can crush bulbar urethra against pubic rami
- other causes
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

Clinical Features
- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder

All patients with suspected urethral injury should undergo RUG

Investigations
- generally will perform RUG or cystoscopy prior to attempt at catheterization

Treatment
- simple contusions
  - no treatment
- partial urethral disruption
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

Complications
- stricture

Infertility and Andrology

Definition
- failure to conceive after 1 yr of unprotected and properly timed intercourse
- incidence
  - 15% of all couples (35-40% female, 20% male, 25-30% combined)

Female Factors

- see Gynecology, GY23

Male Factors

Male Reproduction
- HPTA
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

Etiology
- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumour
  - congenital (Klinefelter's triad: small, firm testes, gynecomastia, and azoospermia)
  - post-infectious (epididymo-orchitis, STIs, viral orchitis especially mumps)
  - uncorrected torsion
  - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery: see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
  - bilateral ejaculatory duct obstruction, epididymal obstructions
  - Kartagener's syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see Endocrinology, E51)
- HPTA (2-3%) e.g. Kallmann's syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery or medications
  - medications
  - prior exposure to chemotherapy or pelvic radiation
  - drugs: cannabis, cocaine, tobacco, alcohol
  - increased testicular temperature (sauna, hot baths, tight pants, or underwear)
  - chronic disease: e.g. liver, renal

History
- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STIs, cryptorchidism
- surgical: vasectomy, herniorrhaphy, orchidopexy, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- FMHx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social Hx: alcohol, tobacco, cocaine, cannabis, school performance/learning disabilities (suggestive of Klinefelter syndrome)
- occupational exposures: radiation, heavy metals

Physical Exam
- general appearance: sexual development, gynecomastia, obesity, pubic hair
- scrotal exam: size, consistency, and nodularity of testicles; palpation of cord for presence of vas deferens; DRE; valsalva for varicocele

Common Terminology on SA
Teratospermia: Abnormal morphology
Asthenospermia: Abnormal motility
Oligospermia: Decreased sperm count
Azoospermia: Absent sperm in semen
Mixed types: e.g. oligoasthenospermia

Mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene is associated with congenital bilateral absence of vas deferens and epididymal cysts, even if patient manifests no symptoms of CF

WHO Guidelines
Male Infertility Factors

SPERM COUNT
Systemic factor/**S**moking
Psychological illness
Endocrinopathy
Retrograde ejaculation
Medications
Chronic disease
Obstructive
Unexplained
Narcotics
Testicular

Normal Semen Values
Volume: 1.5-7.6 mL
Concentration: >15 million sperm/mL
Morphology: 30% normal forms
Motility: >40% adequate forward progression
Liquefaction: complete in 20 min
pH: 7.2-7.8
WBC: <10/HPF or <106 WBC/mL semen

Hypo-gonadal patients interested in fertility preservation should be cautioned against the isolated use of exogenous testosterone and be counseled to pursue treatments that increase endogenous serum testosterone production

Investigations
- SA ≥2 specimens, collected 1-2 wk apart
- hormonal evaluation
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
  - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation
  - chromosomal studies (Klinefelter syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

Treatment
- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco, and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E51)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections
- surgical
  - varicocelectomy (if indicated)
  - vasovasostomy (vasectomy reversal) or epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART)
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - *in vitro* fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

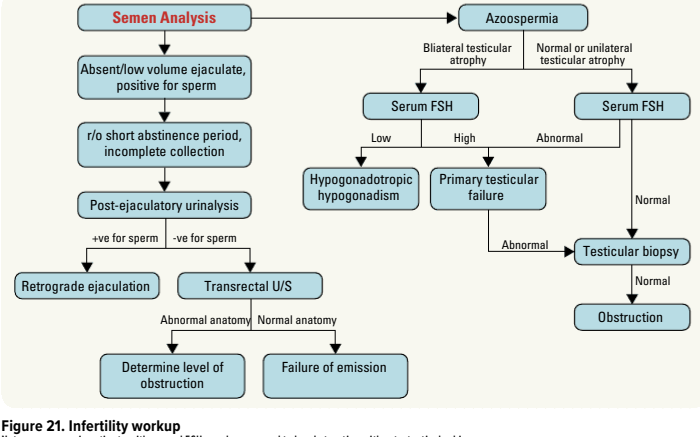


Figure 21. Infertility workup
Note: azoospermic patients with normal FSH may be assumed to be obstructive without a testicular biopsy

Testosterone Deficiency

See Endocrinology, E51

Clinical Features
- sexual: decreased libido, delayed ejaculation, reduced ejaculate volume, decreased orgasm intensity, erectile dysfunction, loss of morning erections, infertility
- cognitive: fatigue, mood changes, depression, insomnia, irritability
- physical: decreased energy, anemia, gynecomastia, hot flashes, decreased muscle mass and increased visceral body fat, osteopenia, testicular atrophy, loss of androgenic hair

Diagnosis
- clinical features ± total testosterone (morning draw) <10 nmol/L
- LH to rule out causes of secondary hypogonadism

Treatment Considerations
- see Endocrinology, E51
- goal: improve quality of life and reduce clinical features while achieving eugonadal testosterone
- if clinical features with normal testosterone
  - rule out depression, hypothyroidism, sleep disorders
  - consider measuring sex-hormone binding globulin and determine free/total testosterone ratio
  - supervised trial of testosterone therapy for three mo (injectable, oral, transdermal patch)
- if low testosterone without clinical features
  - consider other diagnoses: anemia, sarcopenia, chronic glucocorticoid/opioid use, HIV
  - no role for testosterone therapy
  - use aromatase inhibitors, human chorionic gonadotropin, or selective estrogen receptor modulators, in men with testosterone deficiency desiring to maintain fertility.
- in all patients treated with exogenous testosterone: monitor symptoms, adverse events, serum testosterone, hematocrit, and PSA at 3, 6, and 12 mo, then q1yr, DRE recommended at baseline and q1yr

Pediatric Urology

Congenital Abnormalities

- not uncommon; 1 in 200 have congenital abnormalities of the GU tract
- six common presentations of congenital urological abnormalities

1. ANTENATAL HYDRONEPHROSIS

Epidemiology
- 1-5% fetal U/S, some detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

Differential Diagnosis
- transient primary hydronephrosis
- UPJ obstruction
- VUR
- UVJ obstruction or primary non-obstructive megaureter
- ureterocele
- ectopic ureter
- causes of megacystitis (e.g. PUV, Prune Belly syndrome)

Treatment
- antenatal in utero intervention rarely indicated unless evidence of lower urinary tract obstruction with oligohydramnios
- ABx prophylaxis at birth to reduce UTI rates is controversial but may be beneficial to infants with high grade hydronephrosis, dilated ureter, or bladder abnormality. Commonly used ABx include: amoxicillin, cephalexin, and trimethoprim

SFU Grading of Hydronephrosis

Grade 0
No dilation, calyceal walls are opposed to each other

Grade 1 (mild)
Dilation of renal pelvis without dilation of the calyces
No parenchymal atrophy

Grade 2 (mild)
Dilation of renal pelvis and calyces (pelvicalyceal pattern is retained)
No parenchymal atrophy

Grade 3 (moderate)
Moderate dilation of renal pelvis and calyces
Mild calyceal thinning, blunting of fornices, and flattening of papillae

Grade 4 (severe)
Gross dilation of renal pelvis and calyces with loss of borders
Cortical thinning

Note: SFU grading should be supplemented with UTD grading to address the shortcomings of this grading system.

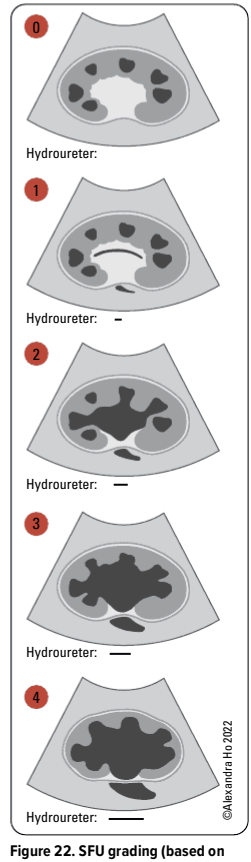


Figure 22. SFU grading (based on ultrasound)

2. POSTERIOR URETHRAL VALVES

Epidemiology
- the most common congenital obstructive urethral lesion in male infants

Pathophysiology
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

Clinical Features
- dependent on age
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), urinary ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within days to weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive; rule out pyloric stenosis, which may present similarly
  - toddlers: UTIs or voiding dysfunction
  - school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

Investigations
- most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened and trabeculated bladder, dilated posterior urethra ("keyhole sign"), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

Treatment
- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

3. URETEROPELVIC JUNCTION OBSTRUCTION

Etiology
- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, aberrant blood vessels
- can rarely be secondary to tumour, stone, etc. in children

Epidemiology
- the most common congenital defect of the ureter
- M:F=2:1
- up to 40% bilateral, which may be associated with worse prognosis

Clinical Features
- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
  - in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl's crisis)

Investigations
- antenatal: serial U/S most common, and renal scan with furosemide

Treatment
- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

4. VESICOURETERAL REFLUX

Definition
- retrograde passage of urine from the bladder, through the UVJ, into the ureter

Classification
- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neuropathic) bladder dysfunction

Epidemiology
- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition

Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life

VUR Grading (based on cystogram)
Grade I: ureters only fill
Grade II: ureters and pelvis fill
Grade III: ureters and pelvis fill with some dilatation
Grade IV: ureters, pelvis, and calyces fill with significant dilatation
Grade V: ureters, pelvis, and calyces fill with major dilatation and tortuosity

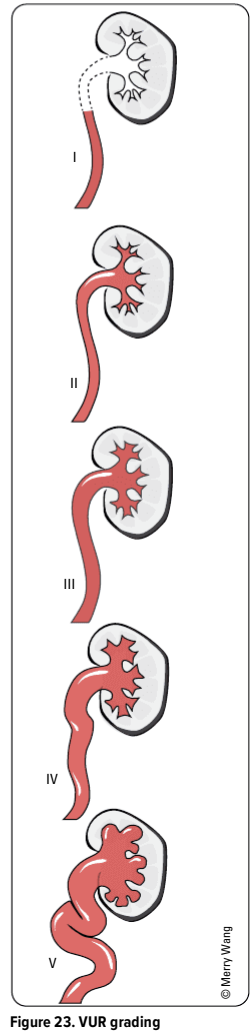


Figure 23. VUR grading (based on cystogram)

Investigations
- focused Hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for infections (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to relatively high incidence of renal scarring
  - height, weight, blood pressure
  - serum Cr
  - U/A, C&S
  - renal U/S
  - DMSA renal scan if at high-risk (greater sensitivity in detecting structural defects associated with dysplasia, renal scarring, or pyelonephritis; entails radiation exposure)
  - sibling family screening is controversial
- diagnose VUR and determine grade with VCUG

Treatment
- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment
- medical treatment: daily ABx prophylaxis at half the treatment dose for acute infection (see *Table 8, U13* – TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
- surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteric injection with bulking agents (Deflux® or Macroplastique®)
  - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux
NEJM 2014;370:2367-2376
Purpose: To determine whether long-term antimicrobial prophylaxis is effective in preventing recurrences of UTI and reducing the likelihood of renal scarring.
Methods: Children with vesicoureteral reflux that were diagnosed after a first or second febrile or symptomatic UTI were randomized to either receive trimethoprim–sulfamethoxazole prophylaxis or placebo.
Results: Prophylaxis reduced the risk of recurrences by 50% and was particularly effective in children whose index infection was febrile and in those with baseline bladder and bowel dysfunction. The occurrence of renal scarring did not differ significantly between the two groups.
Conclusions: Antibiotic prophylaxis given to children with vesicoureteral reflux after a UTI resulted in a reduction of subsequent UTIs, but was not associated with reduced risk of renal scarring.

5. HYPOSPADIAS

Definition
- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream, having intercourse, or depositing sperm in vagina

Epidemiology
- very common; 1 in 300 live male births
- distal hypospadias more common than proximal
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles, or inguinal hernia

Treatment
- eearly surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

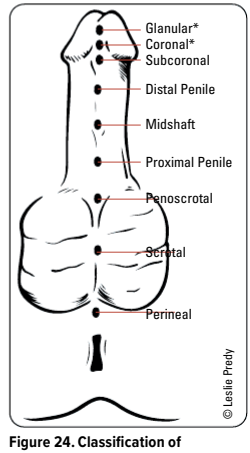


Figure 24. Classification of hypospadias (*account for 75%)

Defer circumcision in patients with hypospadias

6. EXSTROPHY-EPISPADIAS COMPLEX

Definition
- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  - bladder exstrophy: congenital defect of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  - cloacal exstrophy
    - exposed bladder and bowel with imperforate anus
    - associated with spina bifida in >50%
  - epispadias (least severe)
    - urethra opens on dorsal aspect of the penis, often associated with penile curvature

Etiology
- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

Epidemiology
- rare: incidence 1 in 30,000, M:F=3:1 predominance
- high morbidity → multiple reconstructive surgeries, incontinence, infertility, reflux

Treatment
- surgical correction at birth
- later corrections for incontinence, VUR, and low bladder capacity may be needed

Wilms' Tumour (Nephroblastoma)

Etiology
- arises from abnormal proliferation of metanephric blastema

Epidemiology
- 5-10: 5% of all childhood cancers, 5% bilateral, 10% associated with congenital malformation syndromes
- most common primary malignant renal tumour of childhood
- average age of incidence is 3 yr

Clinical Features
- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness (30-40%)
- microscopic hematuria (12-25%)
- nausea/vomiting

Associated Syndromes of Wilms' Tumour

Wilms' aniridia genital anomaly retardation

Beckwith-Wiedemann syndrome

Denys-Drash syndrome

Treatment
- always investigate contralateral kidney and renal vein (for tumour thrombus)
- unilateral disease: radical nephrectomy or nephron-sparing surgery ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

Prognosis
- 5 yr survival 80%

Cryptorchidism/Ectopic Testes

Definition
- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- Denis Browne pouch (between external oblique fascia and Scarpa's fascia) most common
- differential diagnosis:
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

Normal Testicular Development and Descent in Utero

2nd mo: Testicle begins to form

4th mo: Begins to take on its normal appearance and migrates from its origin at the kidney to the internal inguinal ring

7th mo: The testis, surrounded in peritoneal covering, begins to descend through the internal ring, inguinal canal, and external ring to terminate in the scrotum

Epidemiology
- 1.0-4.6% of full term newborns, increased risk in preterms
- 0.7-1.0% at 1 yr

Treatment
- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

Prognosis
- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility, due to Leydig and germ cell loss
  - paternity rates: 33-65%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intra-abdominal > inguinal
  - surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)

Disorders of Sexual Differentiation

Definition
- formerly known as intersex disorders: considered social emergency
- abnormal genitalia for chromosomal sex due to the under-virilization of males or the virilization of females

Classification
1. 46 XY DSD
   - defect in testicular synthesis of androgens
   - androgen resistance in target tissues
   - palpable gonad
2. 46 XX DSD
   - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens

A phenotypic male newborn with bilateral non-palpable testicles should be considered 46 XX with salt-wasting CAH and must undergo proper evaluation prior to discharge

- undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)

3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   - presence of Y chromosome → partial testis determination to varying degrees

Diagnosis
- thorough FMHx noting any consanguinity
- maternal Hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
- P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
- laboratory tests
  - plasma 17-OH-progesterone (after 36 h of life) → increased in CAH
  - plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  - basal adrenal steroid levels
  - serum testosterone and DHT pre- and post-hCG stimulation (2000 IU/d for 4 d)
  - serum electrolytes
  - chromosomal evaluation including sex karyotype
- U/S of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and genitography of urogenital sinus

Treatment
- steroid supplementation as indicated (e.g. CAH)
- sex assignment after extensive family consultation
  - must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
- reconstruction of external genitalia between 6 and 12 mo
- long-term psychological guidance and support for both patient and family

Enuresis

- see Pediatrics, P12

Bladder and Bowel Dysfunction

Definition
- bladder and bowel dysfunction describes voiding and defecation symptoms without a neurogenic or anatomic cause

Clinical Features
- storage symptoms (urgency, frequency, urge incontinence)
- voiding symptoms (hesitancy, slow flow, intermittency)
- gastrointestinal symptoms (constipation and encopresis)

Treatment
- stool softeners (i.e. polyethylene glycol 3350)
- urotherapy and bladder retraining
- pelvic floor physiotherapy
- anticholinergics (solifenacin, propiverine, tolterodine)
- neuromodulation via transcutaneous electrical nerve stimulation

Selected Urological Procedures

Bladder Catheterization

- catheter size measured by the French (Fr) scale – circumference in mm (30 Fr = 1 cm diameter)
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 14-18 Fr)
- should be removed as soon as possible to reduce the risk of UTI

Continuous Catheterization
- indications
  - accurate monitoring of U/O
  - relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  - temporary therapy for urinary incontinence
  - perineal wounds
  - clot prevention (22-24 Fr) for CBI
  - intra- and postoperative
  - comfort for end of life care

Alternatives to Continuous Catheterization
- intermittent catheterization
  - PVR measurement
  - to obtain sterile diagnostic specimens for U/A, urine C&S
  - management of neurogenic bladder or chronic urinary retention
- condom catheter
- suprapubic catheter

Causes of Difficult Catheterizations and Treatment
- patient discomfort → use sufficient lubrication (± xylocaine)
- collapsing catheter → lubrication as above ± firmer or larger catheter (silastic catheter)
- meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
- traumatic injury: repeated prior attempts at catheterization have created traumatic false passage
- BPH → use Coudé catheter as angled tip can help navigate around enlarged prostate (always angle up/anteriorly)
- urethral disruption/obstruction → filiform and followers or suprapubic catheterization
- anxious patient → anxiolytic medication

Complications of Catheterization
- infection: UTI, bladder fistula, bladder perforation (rare)
- meatal/urethral trauma

Contraindications
- trauma: blood at the urinary meatus, scrotal hematoma, pelvic fracture, and/or high riding prostate

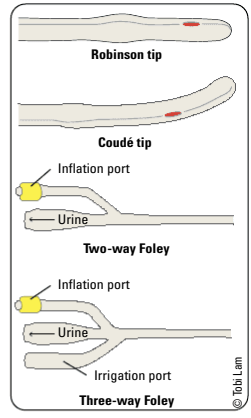


Figure 25. Transurethral (Foley) catheters

Circumcision

Definition
- removal of some or all of the foreskin from the penis

Epidemiology
- 30% worldwide
- frequency varies with geography, religious affiliation, socioeconomic status

Medical Indications
- pathological phimosis and recurrent paraphimosis
- recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
- balanitis xerotica obliterans or other chronic inflammatory conditions

Contraindications
- unstable or sick infant
- congenital genital abnormalities (hypospadias, epispadias, penoscrotal webbing, concealed penis, ventral curvature); may need foreskin to aid in reconstruction
- FMHx of bleeding disorders warrants investigation prior to circumcision

Complications
- early: bleeding, infection, glans injury, amputation, slippage of circumcision device, rarely death
- late: redundant foreskin, cosmetic issues, inclusion cysts, adhesions/skin bridges, suture sinus tracts, ventral curvature, secondary buried penis, phimosis, fistula, meatal stenosis
- 0.6-2% complication rate

Newborn Male Circumcision
Paediatr Child Health 2015;20:311-315
Study: Position Statement by the Canadian Pediatric Society (CPS) reaffirmed Feb 28, 2018
Recommendations: With the exception of some high-risk populations and circumstances where circumcision is indicated for disease prevention, reduction and/or treatment, the routine circumcision of every newborn male is not recommended.

Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men
Cochrane DB Syst Rev 2009;2:CD003362
Purpose: To evaluate the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.
Methods: The analyzed data is from three randomized controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa.
Results: Medical male circumcision reduces the acquisition of HIV by heterosexual men (38-66% over 24 mo).

Vasectomy

Objective
- permanent form of contraception with high probability of reversibility
- no-scalpel vasectomy has lower risks of early postoperative complications than conventional vasectomy
- fascial interposition and cautery of the vas deferens reduce risk of contraceptive failure
- post-vasectomy semen analyses at approximately 3 and 4 mo
- other contraceptive methods should be used post-vasectomy until one azoospermic ejaculate or two consecutive ejaculates with <100,000 immotile spermatozoa

Indications
- fully informed patient desiring permanent surgical sterilization

Complications
- early: infection (0.2-1.5%), bleeding or hematoma (4-20%), primary surgical failure due to recanalization or technical failure (0.2-5%)
- late: chronic scrotal pain (1-14%), delayed vasectomy failure (0.05-1%)
- risk of pregnancy after vasectomy is ~0.1%
- sperm granuloma and congestive epididymitis

Post-vasectomy follow-up
- 1 (or 2) semen analyses at 3 (or 4) mo post-vasectomy
- abandon contraception: if azoospermic or <100,000 immotile sperm at any time post-vasectomy
- re-do vasectomy: if >100,000 immotile sperm or motile sperm on repeat semen analysis 4-8 wk after initial

Cystoscopy

Objective
- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
- scopes can be flexible or rigid
- done under local anesthesia only for vast majority, with no special preparation needed (no NPO, no antibiotics)

Indications
- hematuria
- LUTS (storage or voiding)
- urethral and bladder neck strictures
- bladder stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

Complications
- during procedure (very rare)
  - bleeding
  - anesthetic-related
  - perforation (rare)
- post-procedure (short-term)
  - infections (antibiotic prophylaxis recommended only for high-risk, immunosuppressed)
  - urinary retention
- post-procedure (long-term)
  - stricture

Radical Prostatectomy

Objective
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically, or robotically
  - open surgery is extraperitoneal, minimally-invasive surgery is usually intraperitoneal approach
  - internal iliac and obturator lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicles are also partially or completely removed

Indications
- treatment for localized prostate cancer
  - sometimes done concurrently with radical cystectomy for locally advanced bladder cancer

Complications
- immediate (intraoperative)
  - blood loss
  - rectal injury (extremely rare)
  - ureteral injury (extremely rare)
  - obturator nerve injury (extremely rare)
- perioperative
  - lymphocele formation (if concurrent pelvic lymphadenectomy performed)
  - blood loss
  - urine leak from anastomosis
- late
  - moderate to severe stress urinary incontinence (3-10%)
  - mild stress urinary incontinence (20-30%)
  - ED (~30-50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

Laparoscopic and Robotic-Assisted vs. Open Radical Prostatectomy for the Treatment of Localised Prostate Cancer
Cochrane DB Syst Rev 2017;9:CD009625
Purpose: To compare the effects of laparoscopic radical prostatectomy (LRP) and robotic-assisted radical prostatectomy (RARP) to the retropubic open radical prostatectomy (ORP) in men with localised prostate cancer.
Methods: The review identified two unique RCTs with direct comparison of LRP and RARP to ORP in 446 patients.
Results: When compared to ORP, urinary and sexual quality of life related outcomes appear similar for LRP and RARP. Men who undergo LRP and RARP may have shorter hospital stay (MD -.72, 95% CI -2.19 to -1.25) and require fewer blood transfusions (RR 0.24, 95% CI: 0.12-0.46). The intra- and postoperative complication rates appear similar.
Conclusions: Although there is no high-quality evidence to compare LRP and RARP to ORP in terms of oncological outcomes, patients undergoing LRP or RARP may receive fewer blood transfusions and have shorter hospital stays. The interventions did not differ in terms of urinary and sexual quality of life-related outcomes and serious postoperative complication rates.

Transurethral Resection of the Prostate

Objective
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination
- not a cancer operation
  - standard TURP done with electrocautery (originally monopolar, bipolar also available); newer surgical options for BPH include green-light laser photovaporization, laser enucleation, and minimally-invasive surgical therapies (MIST) such as water-vapour therapy (Rezum™, Uro-Lift™, iTind™, etc.)

Indications
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

Complications
- acute
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called "post-TURP syndrome")
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinusoids, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture

Extracorporeal Shock Wave Lithotripsy

Objective
- to treat renal and ureteral calculi (proximal, middle, or distal) which cannot pass through the urinary tract naturally
  - usually performed under sedation only; no internal instrumentation required; least invasive treatment option but also least successful
- shockwaves focused onto stone using fluoroscopy → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications
- potential first-line therapy for renal calculi <1.5 cm and ureteral calculi
- individuals with calculi in solitary kidney (consider stenting kidney to prevent obstruction)
- patient preference and wait-times play a large role in stone management
  - performed under fluoroscopic-guidance, so stone needs to be radio-opaque (i.e. NOT for uric acid stones)

Contraindications
- acute UTI or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- uncontrolled HTN
- obstruction distal to stone (SWL can be used after stent or nephrostomy inserted)
  - not a contraindication but SWL less successful for very dense stones and in obese patients

Complications
- bacteriuria
- bacteremia
- post-procedure hematuria (common to have mild gross hematuria)
- ureteric obstruction (by stone fragments)
- perinephric hematoma

Transition-Related Surgeries

- ensure appropriate use of gender pronouns
- some procedures require 1 yr trial of hormone therapy, preoperative letters of evaluation and documentation from mental health professionals as outlined by the World Professional Association for Transgender Health Standards of Care – Version 8 guidelines

Table 26. Surgical Options for Gender Transition (Also known as Gender Affirmation Surgery)

Procedure	Description	Follow-Up
Orchiectomy	Scrotal incision and removal of bilateral testicles Scrotectomy in some patients	Eliminates need for testosterone blockers Allows for tuck with great ease
Penile Inversion Vaginoplasty	Formation of vaginal cavity and vulva (clitoris, urethra, mons, labia) using penile and scrotal skin	Lubrication required for penetration Prostate exams conducted vaginally Regular dilation of vaginal cavity to avoid stenosis Complications: granulation tissue, urinary symptoms, fistula formation, hair growth in neovagina
Radial Forearm Phalloplasty Most common technique for phallic reconstruction	Formation of penis using radial forearm graft of skin, blood vessels and nerves Urethral extension ± future penile and testicular implants	High complication rates related to urethral connection (urethral fistula, stricture, post-void dribbling/stream spraying, urinary retention), skin complications and implant issues
Anterolateral Thigh (ALT) Phalloplasty	Formation of penis using skin, blood vessels, nerves and muscular tissue from thigh Urethral extension ± future penile and testicular implants	High complication rate as above Pedicle flap failure very rare Phallus may be very thick due to subcutaneous fat of thigh Sensory recovery may be poorer than radial arm flap
Metoidioplasty	Formation of a penis through release of hormonally-enlarged clitoris from surrounding ligaments Girth added from neighbouring tissue ± urethroplasty ± vaginectomy and scrotoplasty	Lower complication rates when compared to phalloplasty Not capable of penetrative intercourse Major complications may require revision surgery: urethral strictures, urethral fistulas

Common Medications

Table 27. Erectile Dysfunction Medications

Drug	Class	Mechanism	Adverse Effects
sildenafil tadalafil vardenafil (PDE5s for use when some erection present)	Phosphodiesterase 5 inhibitor	Selective inhibition of PDE5 (enzyme which degrades cGMP) Leads to sinusoidal smooth muscle relaxation, increased blood flow and erection	Severe hypotension (very rare) Flushing, headaches, dyspepsia Contraindicated if Hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease) Contraindicated with nitrates
alprostadil (MUSE®), PGE_1 + phentolamine + papaverine mixture	Prostaglandin E_1	Activation of cAMP, relaxing sinusoidal smooth muscle Local release (urethral suppository)	Penile pain Presyncope
alprostadil, papaverine (intracavernosal injection) triple therapy also used: papaverine, phentolamine, PGE_1	See above	See above	Thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) Painful erection Hematoma Contraindicated if Hx of priapism, or in high-risk of priapism

Table 28. Benign Prostatic Hyperplasia Medications

Drug	Class	Mechanism	Adverse Effects
terazosin doxazosin	α_1 blockers	α-adrenergic antagonists reduce stromal smooth muscle tone Reduce dynamic component of bladder outlet obstruction	Presyncope Leg edema Retrograde ejaculation Headache Asthenia Nasal congestion
tamsulosin alfuzosin silodosin	α_{1A} selective		
finasteride dutasteride	5-α reductase inhibitor	Blocks conversion of testosterone to DHT Reduces static component of bladder outlet obstruction Reduces prostatic volume	Sexual dysfunction PSA decreases

Table 29. Prostatic Carcinoma Medications (N>0, M>0)

Drug	Class	Mechanism	Adverse Effects
leuprolide, goserelin *"androgen deprivation therapy"*	GnRH agonist	Initially stimulates LH, increasing testosterone and causing "flare" (initially increases bone pain) Later causes low testosterone	Hot flashes Headache Decreased libido
degarelix	GnRH antagonist	Competitively binds to the pituitary gland GnRH receptors, thereby reducing the release of LH, FSH and consequently testosterone by testes	Back pain Breast enlargement Decreased libido Hot flashes Headache *Slow* or fast heartbeat
*cyproterone acetate	Steroidal antiandrogen	Competes with DHT for intracellular receptors: Prevent flare produced by GnRH agonist Use for complete androgen blockade May preserve potency	
flutamide, bicalutamide	Non-steroidal antiandrogen	As above	Hepatotoxic: AST/ALT monitoring
abiraterone	Non-steroidal antiandrogen	Irreversible cytochrome P450 (CYP) 17 inhibition, blocking synthesis of androgens in tumour, testis, and adrenal glands	Adrenal insufficiency (concurrent treatment with steroids often required) Hypertriglyceridemia Peripheral edema
enzalutamide	Non-steroidal antiandrogen	Androgen receptor signaling inhibitor (full antagonist)	Peripheral edema Fatigue and weakness Hot flashes

*Very rarely used

Table 30. Continence Agents and Overactive Bladder Medications

Drug	Class	Mechanism	Indication	Adverse Effects
oxybutynin	Antispasmodic	Inhibits action of acetylcholine on smooth muscle Decreases frequency of uninhibited detrusor contraction Diminishes initial urge to void	Overactive bladder Urge incontinence + urgency + frequency	Dry mouth Blurred vision Constipation Supraventricular tachycardia
oxybutynin tolterodine trospium solifenacin darifenacin fesoterodine propiverine	Anticholinergic	β-sympathetic receptor blocker in the bladder; relaxes bladder during storage phase	Overactive bladder Urge incontinence + urgency + frequency	As above
mirabegron	β_3 agonist	Sympathomimetic effects: Urinary sphincter contraction Anticholinergic effects: Detrusor relaxation	Overactive bladder Urge incontinence + urgency + frequency	Blood pressure should be monitored
imipramine	Tricyclic antidepressant	Prevents the release of neurotransmitters	Stress and urge incontinence	As above Weight gain Orthostatic hypotension Prolonged PR interval
Botulinum toxin A bladder injections	Neurotoxin	Prevents the release of neurotransmitters	Refractory OAB incontinence both neurogenic and non-neurogenic	Urinary retention, UTI

Note: All anticholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long acting formulations are lacking

Landmark Urology Trials

Trial Name	Reference	Clinical Trial Details
RENAL CANCER		
EORTC-30904	Eur Urol 2011; 59(4):543-552	**Title:** A Prospective, Randomized EORTC Intergroup Phase 3 Study Comparing the Oncologic Outcome of Elective Nephron-Sparing Surgery and Radical Nephrectomy for Low-Stage Renal Cell Carcinoma **Purpose:** Assess the oncologic effectiveness of nephron sparing surgery (NSS) versus radical nephrectomy (RN). **Methods:** 541 patients with small, solitary, low stage tumors suspicious for renal cell carcinoma (RCC) were randomized to NSS and RN. Primary outcome was overall survival. **Results:** Among patients confirmed to have small, solitary, low stage RCC, 10-yr survival was 79.6% for RN and 78.0% for NSS (HR, 1.34; p = 0.17). Only 12 of 117 deaths during follow-up were due to RCC with 4 in RN group and 8 in NSS group. **Conclusions:** Both radical and partial nephrectomy provide excellent oncologic results. In a targeted population of early RCC, there was no significant difference in overall survival.

Trial Name	Reference	Clinical Trial Details
BENIGN PROSTATIC HYPERPLASIA		
PCPT	N Engl J Med 2003;349:215-224	**Title**: The Influence of Finasteride on the Development of Prostate Cancer **Purpose**: To determine whether the drug Finasteride (5-alpha reductase inhibitor) could prevent prostate cancer in men ages 55 and older. **Methods**: 18882 men 55 yr or older with a normal digital rectal examination and a (PSA) level equal to or less than 3.0 ng per milliliter were randomly to receive finasteride (5 mg per day) or placebo for 7 yr. **Results**: There was a 24.8% reduction in prostate cancer prevalence over the 7-yr period among the Finasteride arm compared to the placebo arm (95 % confidence interval, 18.6 to 30.6 percent; P<0.001).However there was a significant increase in high-grade disease among men in the finasteride group compared to the placebo (6.4 % vs. 5.1% P=0.005). **Conclusion**: The PCPT trial in 2003 was the first study to show that a medication (Finasteride) reduces the likelihood of developing prostate cancer. Upon long term follow-up in 2013, this reduction in risk has been attributed to less likelihood of low-grade cancers in men taking finasteride. Although participants who developed prostate cancer while taking finasteride were more likely to have high-grade cancers, this increase was attributed to better detection of disease rather than medication use.
MTOPS	NJEM 2003;349:2387-2398	**Title**: The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia **Purpose**: To determine whether therapy with doxazosin (α-blocker) or finasteride (5α-reductase inhibitor), alone or in combination, would delay or prevent clinical progression of benign prostatic hyperplasia (BPH). **Methods**: Participants were followed-up for a mean time of 4.5 yr to compare the effects of the interventions. The primary outcome was overall clinical progression of BPH (≥4 points from baseline in AUA symptoms score, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent UTI). **Results**: The risk of overall clinical progression was significantly reduced by doxazosin (39% risk reduction, P<0.001) and finasteride (34% risk reduction, P=0.002), as compared with placebo, and the risk was reduced even more with combination therapy (66% for the comparison with placebo, P<0.001) compared with doxazosin (P<0.001) or finasteride (P<0.001) alone. **Conclusions**: Long-term combination therapy with doxazosin and finasteride reduced the clinical progression of BPH significantly more than each therapy alone, as well as reduce the need for invasive therapy in the long term.
BLADDER CARCINOMA		
Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer	NEJM 2003;349:859-866	**Title**: Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer **Purpose**: To evaluate whether the addition of neoadjuvant chemotherapy to radical cystectomy improves outcomes in patients with locally advanced bladder cancer. **Methods**: 317 patients with transitional-cell carcinoma of the bladder (T2N0M0 to T4aN0M0) were randomized to undergo radical cystectomy or to receive three cycles of combined chemotherapy followed by radical cystectomy. **Results**: At 5 yr after treatment initiation, 57% of the combination-therapy group vs. 43% of the cystectomy group were alive (P=0.06). In the combination-therapy group, 38% of the patients were pathologically free of cancer at the time of cystectomy vs. 15% of the cystectomy-only group at the time of surgery (P<0.001). **Conclusions**: For locally advanced bladder carcinoma, neoadjuvant chemotherapy significantly reduces tumour volume which is associated with improved survival.
PROSTATE CANCER		
10 Yr Outcomes After Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer	NEJM 2016;375(15):1415-1424	**Title**: 10 Yr Outcomes After Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer **Purpose**: To evaluate the effectiveness of active monitoring, radical prostatectomy, and radiotherapy in relation to mortality and the incidence of metastases and disease progression. **Methods**: 1643 men randomized into active monitoring, surgery, and radiotherapy. The primary outcome was prostate-cancer mortality at median 10 yr of follow-up and the secondary outcomes were rate of disease progression, metastases, and all-cause deaths. **Results**: No significant difference among groups in prostate-cancer-specific deaths and in the numbers of deaths from any cause. Metastases developed more in the active monitoring group (33 men) vs. surgery group (13 men) or radiotherapy group (16 men) (P=0.004). Higher rates of disease progression in active-monitoring group (112 events) vs. surgery group (46 events) or radiotherapy group (46 events) (P<0.001). **Conclusions**: At 10 yr, prostate-cancer-specific mortality was low regardless of the treatment, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastasis compared to active monitoring.
ERSPC	NJEM 2009;360:1320-1328	**Title**: Screening and Prostate-Cancer Mortality in a Randomized European Study **Purpose**: To determine the reduction of prostate-cancer mortality by PSA-based screening. **Methods**: Participants were randomized to a group that received PSA screening an average of once every 4 yr or to a control group that did not receive such screening. The primary outcome was the rate of death from prostate cancer. **Results**: The incidence of prostate cancer was higher in the screening group than in the control group (8.2% vs. 4.2%). The absolute risk difference was 0.71 deaths/1000 men, meaning that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer. **Conclusions**: PSA-based screening reduced the rate of mortality from prostate cancer by 20% but was associated with a high risk of overdiagnosis.
ERSPC (2014 Update)	Lancet 2014; 384:2027-2035	**Title:** Screening and Prostate Cancer Mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 Years of Follow-Up **Purpose:** Assess benefits of PSA screening with 13 yr follow-up from the ERSPC **Methods:** Multi-centre RCT with predefined central database, analysis, and core age group (55-69 yr) evaluating PSA in 8 European countries. Incidence and mortality truncated at 9, 11, and 13 yr follow-up in the intervention arm was compared to control arm. Primary outcome was prostate cancer mortality in the core age group. **Results:** RR of prostate cancer incidence between intervention and control arms was 1.91 after 9 yr follow-up, 1.66 at 11 yr follow-up, and 1.67 at 13 yr follow-up. RR of PCa mortality was 0.85, 0.78, and 0.79, at 9-, 11-, 13-yr follow-up, respectively. At 13-yr follow-up in the PSA screening group, relative risk reduction is 21%, and absolute risk reduction from death is 1.28 per 1000 men. **Conclusions:** Updated ERSPC data shows PSA screening significantly reduces prostate cancer mortality. This study did not quantify harms and further research required.
CHAARTED	NJEM 2015;373(8):737-46	**Title**: Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer **Purpose**: To assess whether concomitant treatment with Androgen-deprivation therapy (ADT) plus docetaxel would result in longer overall survival than that with ADT alone. **Methods**: Patients with metastatic, hormone-sensitive prostate cancer were randomized to receive either ADT plus docetaxel or ADT alone. The primary objective was overall survival. **Results**: After a median follow-up of 28.9 mo, the median overall survival was 13.6 mo longer in the combination therapy group than within the ADT-alone group (P<0.001). The median time to progression was 20.2 mo in the combination group and 11.7 mo in the ADT-alone group (P<0.001). **Conclusions**: Combination of docetaxel and ADT for hormone-sensitive metastatic prostate cancer resulted in significantly longer overall survival than that with ADT alone.

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VS

Vascular Surgery

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Peripheral Arterial Disease

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Aortic Dissection
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Acronyms

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACEI	angiotensin converting enzyme inhibitor
AKI	acute kidney injury
ALI	acute limb ischemia
ARB	angiotensin II receptor blocker
BMT	best medical therapy
CAS	carotid artery angioplasty + stenting
CCB	calcium channel blocker
CEA	carotid endarterectomy
CEAP	clinical, etiological, anatomical, pathophysiological (classification of venous disease)
CLTI	chronic limb threatening ischemia
CTA	computed tomography angiography
CVA	cerebrovascular accident
CVD	cerebrovascular disease
CVI	chronic venous insufficiency
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
DUS	duplex U/S
Echo	echocardiogram
EVAR	endovascular aortic aneurysm repair
HITT	heparin-induced thrombocytopenia with thrombosis
INR	international normalized ratio
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
MRA	magnetic resonance angiography
MSK	musculoskeletal
PAD	peripheral arterial disease
PFO	patent foramen ovale
PT	prothrombin time
PTT	partial thromboplastin time (i.e. aPTT)
TAA	thoracic aortic aneurysm
TBI	toe-brachial index
TEE	transesophageal echocardiography
TEVAR	thoracic endovascular aortic repair
TIA	transient ischemic attack
U/S	ultrasound

Arterial Disease

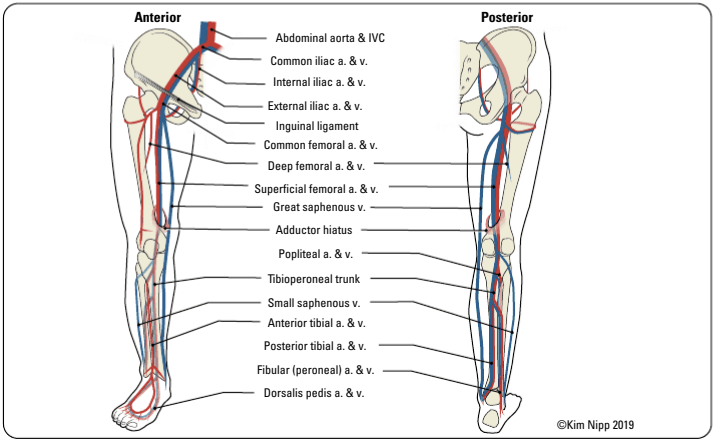

Figure 1. Peripheral vascular anatomy

Acute Limb Ischemia

Definition

- acute occlusion of a peripheral artery that often threatens limb viability with symptom duration <2 wk - clinical presentation usually within h to d
  - urgent management required as skeletal muscle can tolerate 6 h of total ischemia before irreversible damage
  - exception is acute-on-chronic occlusion, where previously developed collaterals provide minimal perfusion
- tends to be lower extremity > upper extremity; femoropopliteal > aortoiliac
- paralysis with complete loss of sensation is sign of late ischemia

Etiology and Risk Factors

- the most common causes of ALI is cardiac embolism; other causes include: thrombosis, peripheral artery aneurysm, dissection, and traumatic artery injury
- embolism
  - cardiac: arrhythmias (most common cause is atrial fibrillation), endocarditis, MI, LV aneurysm, myxoma/cardiac tumour, paradoxical embolism with PFO, valvular heart disease
  - non-cardiac: mural thrombus within arterial aneurysms, atheroembolism, ulcerated plaque with distal embolism
- thrombosis (in situ)
  - progression of high-grade atherosclerotic plaque to acute occlusion
  - bypass graft occlusion (most common etiology of arterial thrombosis in setting of previous open or endovascular reconstruction)
  - hypercoagulable states
    - hypercoagulability, low arterial flow, or hyperviscosity
    - HITT

  - aortic or arterial dissection
    - aortic dissection typically caused by hypertensive crisis
    - isolated arterial dissection of vessels supplying lower limbs is uncommon but can occur from trauma or collagen disorders
  - trauma (e.g. arterial transection, compression)
  - vasospasm/vasculitis
  - iatrogenic (e.g. occlusion at arterial access site)
- differentiating between embolism and thrombosis
  - embolism is more common than thrombosis
  - embolus typically lodges at arterial bifurcations, where the vessel narrows naturally
  - embolism due to plaque rupture generally results in greater degree of ischemia due to relative lack of collaterals
- suspect embolism in patients with the following features:
  - acute onset (patient able to accurately recall the moment of the event)
  - history of embolism
  - known embolic source (e.g. cardiac arrhythmias), lapse in prescribed anticoagulation
  - no prior history of intermittent claudication
  - normal pulse and Doppler U/S or DUS in unaffected limb
- suspect in-situ thrombus in patients with the following features:
  - prior history of intermittent claudication
  - prior vascular intervention/bypass
  - abnormal pulse examination of the unaffected limb

Virschow's Triad
- Hypercoagulability
- Stasis of flow
- Endothelial injury

Clinical Features

- **6 Ps** – may not all be present
  - **P**olar/**P**oikilothermia: cold
    - leg becomes cold
  - **P**allor: pale
    - within a few h becomes mottled cyanosis
  - **P**ain
    - may be constant or elicited by passive movement
    - absent in 20% of cases
  - **P**ulselessness
    - helpful to determine site of occlusion
  - **P**aresthesia (late sign of ischemia)
    - light touch lost first then other sensory modalities
  - **P**aralysis/**P**ower loss (late sign of ischemia):
    - most important; heralds impending non-salvageable limb

Hypercoagulable States

Congenital

Group I (reduced anticoagulants)
- Antithrombin
- Protein C
- Protein S

Group II (increased coagulants)
- Factor V Leiden
- Prothrombin
- Factor VIII
- Other

Sickle cell disease
- Hyperhomocysteinemia

Acquired
- Age
- Obesity
- Smoking
- Immobility
- Cancer
- Pregnancy/systemic hormonal contraceptives
- Antiphospholipid antibody syndrome
- Inflammatory disorders
- Myeloproliferative disorders
- Nephrotic syndrome (acquired deficit in Protein C and S)

Investigations

- history and physical exam are essential: depending on degree of ischemia one may have to forego investigations and go straight to the OR (i.e. an immediately threatened limb)
- DUS: bilateral U/S examination; greater accuracy than pulse examination alone; absent arterial signals in foot indicates threatened limb
- determine Rutherford classification (see *Table 1, VS4*) based on physical findings and Doppler U/S
- ABI: extension of physical exam, easily performed at bedside
- ECG, troponin: rule out recent MI or arrhythmia
- CBC: rule out leukocytosis, thrombocytosis, or thrombocytopenia in patients receiving heparin (may suggest HITT)
- PT/INR, PTT: patient anticoagulated/sub-therapeutic INR
- echo: identify wall motion abnormalities, intracardiac thrombus, valvular disease, or aortic dissection (Type A) (see *Aortic Dissection, VS6*)
- not part of immediate work-up to decide on operative management unlike other tests listed
- CTA: most often used but not a requirement for decision making and sometimes performed after operative intervention; identify underlying atherosclerosis, aneurysm, aortic dissection, embolic sources, emboli in other end organs (e.g. splenic/renal infarcts), and level of occlusion and extent
- angiography: can be obtained in OR as part of intervention or for treatment

Table 1. Rutherford ALI Classification

Category	Description/ Prognosis	Findings		Doppler Signals	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I Viable	Not immediately threatened	None	None	Audible	Audible
II Threatened					
IIa Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
IIb Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Adapted from: Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26:517-38.

Treatment
- immediate unfractionated heparinization with weight-based bolus (70-100 IU/kg) and continuous infusion to titrate PTT to 70-90
- IV fluids, urine output monitoring, analgesia, supplemental O_2
- if impaired neurovascular status: emergent revascularization (Rutherford category IIb)
- if intact neurovascular status: may have time for workup (including CTA)
- identify and treat underlying cause
  - embolus: embolectomy
  - thrombus: thrombectomy ± bypass graft ± endovascular therapy
  - irreversible ischemia (i.e. Rutherford category III): primary amputation or palliation
  - arterial aneurysm: bypass/stent graft
- continue heparin postoperatively; start oral anticoagulant postoperatively when stable x3 mo or longer depending on underlying etiology and other comorbidities
  - note unfractionated heparin carries a greater risk for heparin induced thrombocytopenia than low molecular weight heparin

Complications
- local: compartment syndrome secondary to reperfusion (see Orthopedic Surgery, OR10) with prolonged ischemia; requires 4-compartment (anterior/lateral/superficial and deep posterior) fasciotomy in calf
- heart: risk of arrhythmia, MI, cardiac arrest, and death with reperfusion injury
- kidneys/other organs: renal failure and multi-organ failure due to toxic metabolites from ischemic muscle, rhabdomyolysis
- up to 10% chance of metachronous embolism

Prognosis
- 12-15% mortality rate
- 5-40% morbidity rate (amputation)

Peripheral Arterial Disease

Definition
- chronic ischemia due to inadequate arterial supply to meet cellular metabolic demands during walking (claudication) or at rest (CLTI)

Etiology and Risk Factors
- predominantly due to atherosclerosis (for pathogenesis, see Cardiology and Cardiac Surgery, C30); primarily occurs in the lower extremities
- modifiable risk factors: smoking, DM, hyperlipidemia, HTN, obesity, and sedentary lifestyle
- non-modifiable risk factors: advanced age, and PMHx or FMHx of PAD/CAD/CVD

Clinical Features
- claudication:
  1. pain with exertion: usually in calves or any exercising muscle group
  2. relieved by short rest: less than 5 min and no postural changes necessary
  3. reproducible: same distance or time to elicit pain, same location of pain, same amount of rest to relieve pain
  4. an asymptomatic pulse deficit: this mandates medical management
     - the presence of the preceding features differentiates vascular claudication from neurogenic claudication or MSK pain
- CLTI:
  1. includes rest pain, night pain, and/or tissue loss (ulceration or gangrene) in a patient with existing PAD for at least 2 wk

Distinction between CLTI and ALI

ALI: A precipitous decrease and/or cessation in blood flow to a limb threatening viability. Typically, due to arterial embolism or thrombosis, or other acute cause. Characterized by rapidly worsening leg pain that is present for <2 wk (usually h to d); may occur in patients with or without history of claudication

CLTI: Severe manifestation of PAD where blood flow to the extremities is markedly reduced. Defined as ischemic foot pain at rest or at night, occurring >2 wk, wounds, or gangrene in patients who may (or may not) have a history of claudication

Acute Aortoiliac Occlusion
If a patient presents with new onset bilateral ALI, suspect possible occlusion of the aorta or aortoiliac segment. Etiologies include thrombosis or rupture of AAA, aortic dissection, or large saddle embolism

2. pain most commonly over the forefoot/toes, waking person from sleep, and often relieved by hanging foot off bed
3. ankle pressure 50 mmHg, toe pressure <30 mmHg, and/or ABI <0.40
   - distal pulses are absent
   - signs of poor perfusion: hair loss, hypertrophic nails, shiny skin, atrophic muscle, ulcerations and infections, slow capillary refill, prolonged pallor with elevation and rubor on dependency, and venous troughing (Buerger's sign/Buerger's angle) (collapse of superficial veins of foot)
4. high-risk of 1 yr limb amputation (25%) and mortality (25%)
5. usually the result of multilevel occlusive arterial disease in the lower extremity

Investigations

- routine blood work, fasting metabolic profile
- ankle pressure and ABI: highest ankle pressure (dorsalis pedis or posterior tibial) for each side divided by highest brachial pressure (see *Table 2 for Cut-Offs*)
- toe pressure and TBI: highest pressure in the great toe for each side divided by highest brachial pressure; useful in patients with non-compressible vessels
- ABI and/or a TBI study are recommended to confirm diagnosis of PAD
- arterial DUS: combines b-mode and Doppler U/S to visualize blood vessels and characterize flow and plaques
- non-invasive: CTA and MRA excellent for large arteries (aorta, iliac, femoral, popliteal) but may have difficulty with tibial arteries (especially in the presence of significant wall calcification)
  - requires IV injection of iodinated contrast for CTA (contrast-induced nephropathy risk), gadolinium for MRA (avoid in patients with severe renal failure)
  - used primarily for planning interventions
- invasive: arteriography
  - superior resolution to CTA/MRA, better for tibial arteries, can be done intraoperatively as part of intervention
  - can be diagnostic and/or therapeutic

Table 2. Ankle-Brachial Index Cut-Offs

ABI Recording	Degree of PAD
>1.30	Non-compressible vessel (e.g. wall calcification, common in DM)
0.91-1.30	Normal
0.71-0.90	Mild
0.50-0.70	Moderate
<0.5	Severe

Treatment

- goals
  - preserve viability (save the leg)
  - preserve life (avoid complicated procedures in sick patients)
  - improve function and alleviate symptoms
  - prevent deterioration and recurrence
- conservative
  - risk factor modification (smoking cessation, glucose control, treatment of HTN and hyperlipidemia)
  - structured exercise program (30-45 min 3x/wk): improves collateral circulation and muscle oxygenation
  - foot care (especially in DM): trim toenails, check between toes for skin breaks, wear socks and shoes, clear shoes of any debris, keep wounds clean/dry, avoid trauma and pressure on wounds
- pharmacotherapy
  - for global cardiovascular protection since patients with PAD are at increased risk for CAD and CVD
  - antiplatelet agents (e.g. ASA, clopidogrel)
  - anticoagulants (e.g. low-dose rivaroxaban)
  - statin ± icosapent ethyl
  - ACEI/ARB
  - SGLT-2 inhibitor if HbA1c >7%
- surgical
  - indications: severe lifestyle impairment, vocational impairment, CLTI
  - revascularization
    - endovascular (angioplasty ± stenting, may also include atherectomy in select cases)
    - endarterectomy: removal of plaque and repair with patch (usually distal aorta or common/deep femoral)
    - bypass graft sites:
      - anatomic: aortofemoral, femoropopliteal, femorotibial bypass, popliteal-tibial bypass
      - extra-anatomic: axillofemoral, femorofemoral
    - graft choices: saphenous vein graft (reversed or in situ), synthetic (polytetrafluoroethylene graft, e.g. Gore-Tex® or Dacron®), cryo-preserved homograft
    - not offered to asymptomatic patients

Leriche Syndrome
Chronic aortoiliac occlusive disease presenting with a triad of:
1. Claudication (of buttocks and thighs)
2. Decreased femoral pulses
3. Erectile dysfunction/impotence

Subclavian Steal Syndrome
A chronic arterial disease of the upper limb where stenosis or occlusion of the proximal subclavian artery results in retrograde flow from the vertebral artery, compromising vertebrobasilar circulation. Patients can present with pre/syncope and neurological deficits especially upon exertion of the limb (rare)

Differential Diagnosis of Lower Extremity Pain

Vascular
- Atherosclerotic disease
- Fibromuscular dysplasia
- Popliteal entrapment syndrome
- Venous claudication/hypertension

Neurogenic
- Neurospinal disease (e.g. spinal stenosis)
- Complex regional pain syndrome
- Radiculopathies
- Diabetic neuropathy

MSK
- Osteoarthritis
- Rheumatoid arthritis/connective tissue disease
- Remote trauma
- Medial tibial stress syndrome
- Sprain/strain

Treating PAD
Note that symptoms do not necessarily correlate with ABI measurement, e.g. a patient with ABI of 0.45 may be asymptomatic. Intervention is guided mainly by the patient's clinical presentation

The ABCDEs of PAD Treatment
ANTI-PLATELET (ASA, clopidogrel), anti-coagulant (low dose rivaroxaban),
ACEI/ARB
BP control; target sBP <140 mmHg, β-blocker (if indicated)
Cholesterol management (statin); target LDL-C <2 mmol/L, smoking cessation
Diabetic control; target HbA1c <7%, diet/weight management
Exercise (3x/wk, 30-45 min per session)

- amputation: if not anatomically suitable for revascularization, persistent infections/gangrene, unremitting rest pain that is poorly controlled with analgesics, medically unfit for revascularization
- chronic pain clinic referral: if not anatomically suitable or clinically fit for revascularization but has persistent unremitting rest or night pain

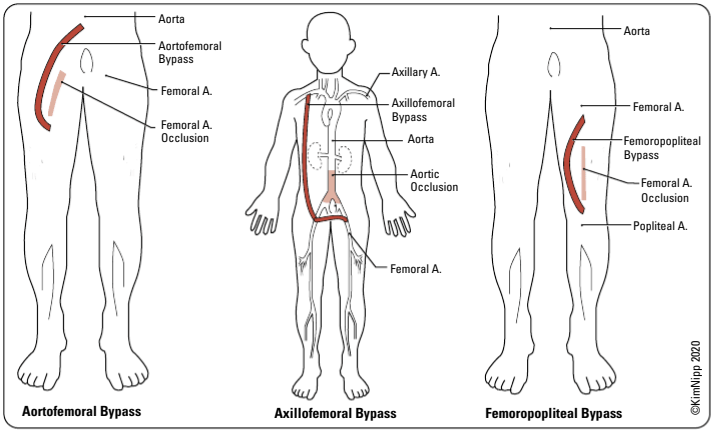

Figure 2. Aortofemoral bypass, axillofemoral bypass, and femoropopliteal bypass

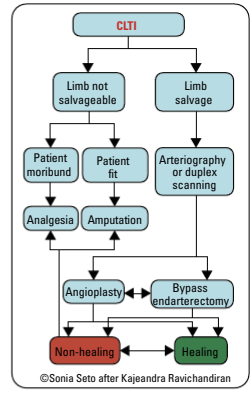

Figure 3. Treatment options for CLTI
Modified from Beard JD. Chronic lower limb ischemia
BMJ 2000;320:854-857

Prognosis

- claudication: conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 yr, <4% will require amputation
- for patients with CLTI, at 1 yr: 25% risk of mortality (secondary to CVA/MI), 25% risk of major amputation, 50% alive with two limbs, 33% 5 yr survival rate

Aortic Disease

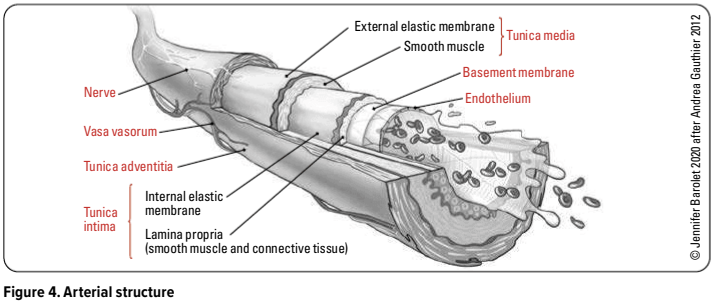

Figure 4. Arterial structure

Aortic Dissection

Definition

- tear in aortic intima allowing blood to dissect into the media
- Stanford classification: Type A (involving the ascending aorta) vs Type B (involving the aorta distal to the left subclavian artery)
- acute <2 wk (initial mortality 1% per h for Type A dissections)
- chronic >2 wk

Etiology

- most common: chronic and/or uncontrolled HTN
- other: connective tissue disease (e.g. Marfan syndrome, Ehlers-Danlos type IV syndrome), cystic medial necrosis, atherosclerosis, congenital conditions (e.g. coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection (e.g. syphilis), trauma, arteritis (e.g. Takayasu's)

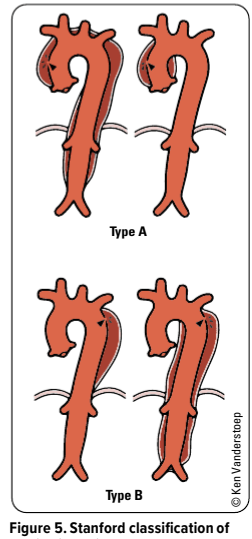

Figure 5. Stanford classification of aortic dissection

Epidemiology
- M:F=3:1
- small increased incidence in African-Canadians (related to higher incidence of HTN); lowest incidence in Asians
- peak incidence: ages 50-65; ages 20-40 with connective tissue diseases

Clinical Features
- sudden onset tearing chest or back pain that radiates distally or between the scapulae with:
  - HTN
  - ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotids (ischemic stroke, partial Horner's syndrome), splanchnic (mesenteric ischemia), renal (AKI), peripheral (ischemic leg), intercostal vessels (spinal cord ischemia)
  - "unseating" of aortic valve cusps (new diastolic murmur in 20-30%) in Type A dissection can lead to severe aortic insufficiency
  - rupture into pleura (dyspnea, hemoptysis), retroperitoneum (hypotension, shock), or pericardium (cardiac tamponade in Type A dissection)
  - syncope

Investigations
- CTA: mainstay for diagnosis and determining type and extent of dissection; MRA may be used if CTA is contraindicated
- ECG: rule out cardiac causes (e.g. LV hypertrophy ± ischemic changes, pericarditis, heart block, MI)
- CXR: widened mediastinum, hemothorax if ruptured, apical pleural cap
- TEE: rule out intra-cardiac thrombus
- consider: lactate (elevated in ischemic gut, shock), amylase (rule out pancreatitis), troponin (rule out MI), CBC, electrolytes, creatinine (renal failure), LFTs (shock, liver)

Treatment
- Type A dissection needs referral to cardiac surgeon for urgent repair
  - resection of segment with intimal tear; reconstitution of flow through true lumen; replacement of the affected aorta with prosthetic graft
  - postoperative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
  - perioperative mortality amongst surgically treated patients is estimated as 17-22%
  - initial mortality rate without surgery is 1% per h for first 24 h, 30% 1 wk, 80% 2 wk
- Type B dissection is usually managed medically in the absence of spinal/mesenteric/limb malperfusion syndrome
  - <10-20% require urgent operation for complications
  - acute therapy is typically with intravenous antihypertensives titrated to sBP of 100-120 mmHg measured by arterial line and HR of 50-65 bpm in critical care setting
  - may transition to oral meds after initial control
  - β-blocker to lower BP and decrease cardiac contractility (e.g. labetalol); nondihydropyridine CCB (e.g. diltiazem) if clear contraindications to β-blockers, and as second-line therapy; IV nitroglycerin also used as second-line agent
  - ACEI and/or other vasodilators if insufficient BP or HR control
  - selective intervention (endovascular or surgical) for complications or refractory symptoms/progression despite medical therapy
  - may be a subset of patients who could be well treated with early aortic stent-grafting after initial medical stabilization
  - with treatment, 60% 5 yr survival, 40% 10 yr survival
  - long term complications include aneurysmal degeneration of the aorta
- Type B dissection with spinal/mesenteric/renal/limb malperfusion and/or aortic rupture may be treated with TEVAR or open surgical repair

Aortic Aneurysm

Definition
- localized dilatation of an artery >1.5x normal diameter (3 cm and larger for abdominal aorta)
- true aneurysm: involves all vessel wall layers (intima, media, adventitia)
- false aneurysm (pseudoaneurysm): does not involve all layers; breach in intima/media that allows blood to collect between media and adventitia
- aneurysms can rupture, thrombose, embolize, erode, and fistulize

Classification
- shape
  - fusiform: concentric; involves full circumference of vessel wall
  - saccular: eccentric; involves only a portion of vessel wall (theoretical higher risk of rupture due to unequal distribution of pressure)
- location
  - TAA: ascending, transverse arch, descending
  - thoracoabdominal

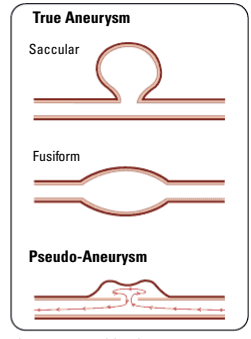

Figure 6. Classification of aneurysms

Ruptured AAA

Classic Triad
Hypotension/collapse
Back/abdominal pain
Palpable, pulsatile abdominal mass (caution in patients with raised BMI)

Initial Management
Intravenous access with two peripheral large bore IVs
Permissive hypotension (sBP enough to maintain mental status)

- AAA: 90-98% are infrarenal
  - suprarenal: starts above the renal arteries but does not involve the thoracic aorta
  - pararenal: starts at the renal arteries but the superior mesenteric artery origin is not aneurysmal
  - juxtarenal: starts immediately distal to renal arteries (there is no normal aorta immediately distal to the origin of the renal arteries); renal artery origin is not aneurysmal
  - infrarenal: starts distal to the renal arteries (there is some normal aorta immediately distal to the origin of the renal arteries)

Etiology and Risk Factors

- risk factors: smoking (current or prior), advanced age, male sex, White race, FMHx, presence of other large vessel aneurysms, HTN
- degenerative
- traumatic
- mycotic (Salmonella, Staphylococcus, usually suprarenal aneurysms)
- connective tissue disorder (Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos type IV syndrome)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic aneurysms are associated with bicuspid aortic valve
- aortic dissection
- congenital (e.g. Turner's syndrome)

Clinical Features

- 75% asymptomatic
- most commonly in the abdominal aorta
- clinical diagnosis of ruptured AAA includes the classic triad of abdominal/back pain, hypotension, pulsatile abdominal mass
- common presentation: due to acute expansion or rupture
  - syncope
  - pain (chest, abdominal, flank, back)
  - hypotension
  - palpable pulsatile mass at or above the umbilicus
  - airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis (indicates thoracic or thoracoabdominal aortic aneurysm)
  - distal pulses may be intact

Investigations

- blood work: CBC, electrolytes, urea, creatinine, PTT, INR, blood type, and crossmatch
  - if ruptured AAA: the only essential bloodwork is type and cross
- abdominal U/S (approaching 100% sensitivity, up to ± 0.6 cm accuracy in size determination) – useful for screening and surveillance
- CT with contrast (accurate anatomic visualization, size determination, EVAR planning)
- peripheral arterial DUS (rule out aneurysms elsewhere, e.g. popliteal)

Treatment

- conservative (for asymptomatic aneurysms that do not meet the size threshold for repair; see below)
  - cardiovascular risk factor reduction: smoking cessation; control of HTN, DM, hyperlipidemia, regular exercise, watchful waiting, U/S surveillance with frequency depending on size and location
- surgical
  - indications
    - ruptured
    - symptomatic (tenderness on palpation of the aneurysm)
    - AAA: size >5.5 cm (men) or >5.0 cm (women)
    - rapid growth greater than 0.5 cm/6 mo or 1 cm/yr
    - saccular aneurysm
    - pseudoaneurysm
    - mycotic
  - risk of rupture depends on: size, family history of rupture, rate of enlargement (>1 cm/yr in diameter), symptoms, and comorbidities (HTN, COPD, dissection), smoking
  - surgical options for AAA
    - open surgery (transperitoneal (anterior) or retroperitoneal)
      - complications
  - early: renal failure, spinal cord injury (paraparesis or paraplegia), impotence, arterial thrombosis, anastomotic rupture or bleeding, peripheral emboli, ischemia
  - late: graft infection/thrombosis, aortoenteric fistula, anastomotic (pseudo)aneurysm
  - death (2-5%)
    - EVAR
      - newer procedure
      - advantages: preferred to open surgery in higher risk patients with suitable anatomy; decreased perioperative morbidity and mortality, procedure time, need for transfusion, ICU admissions, length of hospitalization, and recovery time

Canadian Society of Vascular Surgery 2020 AAA Screening Guidelines
Recommend:
Can J Surg 2021; 64(5):E461-466
One time screening U/S for:
- Men age 65-80
- Women age 65-80 with smoking history or cardiovascular disease
- Individuals age >55 who are first degree relatives of persons with AAA
- Individualized screening for men and women age >80 based on life expectancy and patient preference
- Repeat ultrasound 10 yr after initial screening if aortic diameter 2.5-3 cm

- disadvantages: endoleak rates as high as 20-50%, device failure increasing as longer follow-up periods are achieved, re-intervention rates 10-30%, cost-effectiveness is an issue, radiation exposure (especially in younger patients due to need for life-long follow-up)
- complications
  - early: immediate conversion to open repair (<1%), groin hematoma, arterial thrombosis, iliac artery rupture and thromboemboli, renal failure, impotence, ischemia
  - late: endoleak, graft kinking, stent fracture, device component separation and migration, thrombosis, rupture of aneurysm, complications of radiation exposure, infection
  - death (1-2%, though may be up to 10% in elective advanced endovascular repair especially with proximal aortic and thoracoabdominal repairs)

Carotid Stenosis

Definition

- narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids (carotid bulb)

Risk Factors

- HTN, smoking, DM, CVD or CAD, dyslipidemia, older age

Clinical Features

- may be asymptomatic
- if symptomatic: TIA, ischemic stroke; may be hemispheric presentation (deficits contralateral to carotid lesion) or ocular presentation (deficits ipsilateral to carotid lesion – amaurosis fugax or retinal artery ischemia)
- physical exam
  - fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)

Investigations

- CBC, PT/INR, PTT (hypercoagulable states)
- ECG, echo (rule out other causes of stroke)
- carotid duplex U/S or DUS: determines severity of disease (mild/moderate/severe stenosis or occlusion)
- angiography: CTA, MRA

Treatment

- generally the decision to treat with BMT alone vs. BMT + surgical management depends on whether stenosis is asymptomatic or symptomatic (see *Table 3, VS10*); size of infarct, patient functional recovery, life expectancy, and comorbidities are important in decision-making
- symptomatic carotid stenosis is defined as focal neurologic deficits referable to carotid artery distribution occurring within the past 6 mo with >50% stenosis; ideally surgical treatment should be done within the first 48 h to 2 wk of symptom onset
- lifestyle modifications: smoking cessation, weight loss, dietary changes, exercise

1. medical management

- anti-hyperglycemics: if concomitant DM
- anti-hypertensives: target BP <140/90 or <140/85 if concomitant DM
- statins: aggressive management to achieve LDL-C reduction; plaque stabilization effect
- anti-platelet agents (ASA ± clopidogrel): confer ~25% relative risk reduction
- smoking cessation

2. surgical management

- CEA or CAS for symptomatic carotid stenosis
- CEA: generally mainstay of treatment
- CAS: indicated if poor surgical access, radiation-induced stenosis, or comorbidities that increase risk of surgery/anesthesia
- aggregate risk of death, stroke, or MI in periprocedural period is not significantly different between CEA or CAS
  - higher risk of periprocedural stroke in CAS
  - higher risk of MI and temporary cranial nerve palsy in CEA

10 Yr Stroke Prevention after Successful Carotid Endarterectomy for Asymptomatic Stenosis (ACST-1): A Multicentre Randomised Trial
Lancet 2010;376:1074-1084
Purpose: Assess the long-term effects of successful CEA.
Methods: 3120 asymptomatic patients with significant carotid artery stenosis generally ≥60% were randomized to immediate CEA and indefinite deferral of CEA. Primary outcomes were perioperative mortality and morbidity (death or stroke within 30 d) and non-perioperative stroke.
Results: Perioperative risk of stroke or death within 30 days was 3.0% (95% CI, 2.4-3.9%) with no difference between groups. Excluding perioperative events and non-stroke mortality, 10 yr stroke risks were 10.8% (immediate CEA) versus 16.9% (deferred CEA) (P=0.0004).
Conclusions: In asymptomatic patients under age 75 with significant carotid artery stenosis, successful CEA reduces the 10 yr stroke risk. Net benefit depends on risks from unoperated carotid lesions, future surgical risks, and whether life expectancy exceeds 10 yr.

Second Asymptomatic Carotid Surgery Trial (ACST-2): A Randomized Comparison of Carotid Artery Stenting Versus Carotid Endarterectomy
Lancet 2021;398:1065-1073
Purpose: Compare long-term outcomes for CAS versus open CEA in patients with significant asymptomatic carotid stenosis.
Methods: 3625 asymptomatic patients with carotid artery stenosis ≥60% were randomized to CAS and CEA with mean follow-up of 4.9 yr. Primary outcomes were procedural mortality and morbidity, and non-procedural stroke.
Results: 1% had disabling stroke or death procedurally (15 allocated to CAS and 18 to CEA) and 2% had non-disabling procedural stroke (48 allocated to CAS and 29 to CEA). 5 yr non-procedural stroke rates were 2.5% in each group for fatal or disabling stroke, and 5.3% for CAS versus 4.5% with CEA for any stroke (P=0.33)
Conclusions: Occurrence of serious complications after CAS and CEA is similar and uncommon, and both procedures have similar long-term effects on fatal and disabling stroke.

Table 3. Indications for Medical vs. Surgical Management of Carotid Stenosis

Stenosis	Asymptomatic	Symptomatic
<50%	BMT	BMT
50-60%	BMT	
60-70%	BMT + Surgical management if: • Progression of disease • Young and otherwise healthy • Ocular ischemic syndrome • Life expectancy >5 yr • Surgeon's perioperative morbidity/mortality risk <3% 60-99% stenosis: ARR=1-3%; NNT~33	BMT + Surgical management if: Surgeon's perioperative morbidity/mortality risk <3% 50-70% stenosis: ARR=4.6%, NNT=22
70-99%	BMT + Surgical management if: Surgeon's perioperative morbidity/mortality risk <3% ARR=1-3%; NNT~33	BMT + Surgical management if: Surgeon's perioperative morbidity/mortality risk <3% ARR=16%; NNT~6
100%	BMT No surgical intervention	BMT No surgical intervention

ARR = absolute risk reduction; NNT = number needed to treat

Venous Disease

Venous Thromboembolism

- see Hematology, H36

Chronic Venous Insufficiency

Definition

- wide spectrum of chronic venous disease with advancing symptoms of edema, skin changes, varicosities, or leg ulcers

Epidemiology

- primary venous insufficiency is the most common venous disorder of the lower extremities
- 65% of North American adult population develops some degree of venous insufficiency

Etiology

- spectrum of chronic venous disease involving deep and superficial lower extremity veins caused by calf muscle pump dysfunction, venous obstruction, and chronic valvular incompetence (reflux) due to phlebitis, varicosities, or DVT
- final common pathway is development of venous hypertension, leading to histologic and physiologic inflammatory changes
- primary (99% of cases) venous insufficiency: venous valve incompetence or obstruction
  - suspected risk factors: increasing age, systemic hormonal contraceptive use, prolonged standing, pregnancy, obesity
- secondary venous insufficiency: DVT, malignant pelvic tumours with venous compression, congenital anomalies, arteriovenous fistulae, trauma, pregnancy (rare)

Clinical Features and Complications

- pain (most common) described as fullness/tightness and aching; worst at end of the day
- telangiectasias or reticular veins: dilated intradermal and subdermal veins, respectively (<3 mm in diameter) (see *Table 4, CEAP Classification of Venous Disease, VS11*)
- varicose veins: visible, long, dilated, and tortuous superficial veins (great or small saphenous veins and tributaries) resulting from incompetent valves in the deep, superficial, or perforator systems (>3 mm in diameter) (CEAP C2)
- ankle and calf edema; relieved by foot elevation (CEAP C3)
- burning, aching, fullness/tightness
- skin changes:
  - eczema, stasis dermatitis, pruritus, brownish hyperpigmentation (hemosiderin deposits) (CEAP C4a)
  - subcutaneous fibrosis if chronic (lipodermatosclerosis or "inverted champagne bottle legs"), atrophie blanche (CEAP C4b)

- ulceration: shallow, above medial malleolus (gaiter area), weeping (wet), painless, irregular outline:
  - healed venous ulcer (CEAP C5)
  - active venous ulcer (CEAP C6)
- recurrent superficial thrombophlebitis and DVT
- bleeding or hematoma of varicosities secondary to trauma

Table 4. CEAP Classification of Venous Disease

Clinical		Etiological		Anatomical		Pathophysiological	
C0	No clinical signs of disease	Ec	Congenital	As	Superficial veins	Pr	Reflux
C1	Telangiectasia or reticular veins	Ep	Primary	Ap	Perforating veins	Po	Obstruction
C2	Varicose veins	Es	Secondary	Ad	Deep veins	Pr,o	Reflux + obstruction
C3	Edema	En	No etiology identified	An	No venous location identified	Pn	No pathophysiology identified
C4: C4a C4b	Skin changes: Eczema, pigmentation Lipodermatosclerosis or atrophie blanche						
C5	Healed venous ulcers						
C6	Active venous ulcers						
S	Symptomatic						
A	Asymptomatic						

Investigations
- ABI (pre-compression to ensure no arterial disease)
- venous Doppler U/S or DUS

Treatment
- conservative
  - elastic compression stockings, ambulation, periodic rest-elevation, avoid prolonged standing
  - ulcers: wound care using multilayer compression bandage ± antibiotics ± debridement PRN
  - medical treatments are variable, e.g. pentoxifylline for venous ulcer healing, flavonoids (e.g. diosmin) for pain, etc.
- surgical
  - surgical destruction of vein with partial or complete removal; techniques include vein ligation/stripping, phlebectomy, perforator ligation
- indications for surgery:
  - documented reflux at the saphenofemoral or saphenopopliteal junction by DUS or Doppler U/S
  - failed trial of conservative treatment for >3 mo
  - signs of CVI (eczema, pigmentation, lipodermatosclerosis, ulceration) or complications associated with varicosities (ulceration due to venous stasis, hemorrhage from superficial varicosity, recurrent superficial thrombophlebitis, stasis dermatitis, varicose eczema, lipodermatosclerosis, unremitting edema/pain affecting quality of life and requiring chronic analgesia)
- 10 yr postoperative recurrence of 20%
- endovenous: laser therapy, radiofrequency ablation, foam/liquid/glue sclerotherapy

Lymphedema

Definition
- impaired lymphatic drainage resulting in accumulation of interstitial fluid and fibroadipose tissue

Etiology
- primary
  - congenital lymphedema (e.g. Milroy disease, Turner syndrome): presents age <2
  - lymphedema praecox (75% of primary cases): presents in adolescence at onset of puberty
  - lymphedema tarda: presents age >35
- secondary
  - infection: filariasis (roundworm parasitic infection; leading cause worldwide), cellulitis, lymphadenitis, tuberculosis
  - inflammation: rheumatoid arthritis, dermatitis, psoriasis, sarcoidosis
  - malignant infiltration/obstruction: axillary, groin or intrapelvic, pressure from large tumours
  - iatrogenic: radiation/surgery (axillary, groin lymphadenectomy) (leading cause in North America), vein surgery, lymph node dissection, scarring
    - patients who develop lymphedema after axillary lymph node dissection are at increased risk for developing angiosarcoma
  - traumatic injury and burns
  - venous disease: CVI

Clinical Features
- classically non-pitting edema and hyperkeratotic cutaneous/subcutaneous changes with progressive disease
- impaired limb mobility, discomfort/pain, psychological distress
- positive Stemmer sign (sensitive): examiner unable to lift skin of thickened skin fold at the base of second toe or finger
- lipodermatosclerosis
- ulcerations

Investigations
- lymphoscintigraphy: most definitive test
- secondary causes of lymphedema must be evaluated and treated appropriately if found

Treatment
- conservative measures: avoid limb injury, treat skin infections early, skin hygiene, limb elevation, avoid prolonged sitting/standing/crossing legs
- external support: intensive (compression bandages) vs. maintenance (compression garments)
- exercise: gentle daily exercise of affected limb, gradually increasing range of motion (must wear compression garment while exercising)
- massage: manual lymph drainage therapy
- surgical: physiological (early disease: increase lymphatic drainage) lymphovenous bypass vs. reductive (advanced disease: remove fibroadipose deposits)

Landmark Vascular Surgery Trials

Trial Name	Reference	Clinical Trial Details
ARTERIAL DISEASE		
BASIL	J Vasc Surg 2010;51(5 Suppl):5S-17S	**Title**: Bypass vs. Angioplasty in Severe Ischemia of the Leg (BASIL) Trial: An Intention-to-Treat Analysis of Amputation-Free and Overall Survival **in** Patients Randomized to a Bypass Surgery (BSX)-First or a Balloon Angioplasty (BAP)-First Revascularization Strategy **Purpose**: Determine the optimal first line revascularization surgery between bypass surgery and balloon angioplasty in severe leg ischemia. **Methods**: 452 enrolled patients in 27 United Kingdom hospitals, half were randomised to BSX-first and half to BAP-first. All patients were monitored for 3 yr and more than half were monitored for >5 yr. **Results**: AFS (Amputation Free Survival) and OS (Overall Survival) did not differ between treatments during follow-up. BSX-first patients who survived 2 yr post randomization had a reduced hazard ratio for subsequent AFS of 0.85% (CI, 0.5 to 1.07; P=0.108) and for subsequent OS of 0.61% (95% CI, 0.50 to 0.75; P=0.009) in an adjusted time-dependent Cox proportional hazards model. **Conclusions**: No significant difference in amputation-free survival and overall survival between severe limb ischemia patients treated with bypass surgery and those treated with balloon angioplasty.
BASIL-2	The Lancet 2023; 401:1798-1809	**Title**: A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial **Purpose**: To compare the effectiveness of a vein bypass first with a best endovascular treatment first revascularization strategy in terms of preventing major amputation and death in patients with chronic limb threatening ischemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularization procedure to restore limb perfusion. **Methods**: Between July 22, 2014, and Nov 30, 2020, 345 participants with chronic limb-threatening ischemia were enrolled in the trial and randomly assigned: 172 (50%) to the vein bypass group and 173 (50%) to the best endovascular treatment group. **Results**: Major amputation or death occurred in 108 (63%) of 172 patients in the vein bypass group and 92 (53%) of 173 patients in the best endovascular treatment group (adjusted hazard ratio [HR] 1·35 [95% CI 1·02–1·80]; p=0·037). In both groups the most common causes of morbidity and death, including that occurring within 30 days of their first revascularization, were cardiovascular (61 deaths in the vein bypass group and 49 in the best endovascular treatment group) and respiratory events (25 deaths in the vein bypass group and 23 in the best endovascular treatment group; number of cardiovascular and respiratory deaths were not mutually exclusive). **Conclusions**: A best endovascular treatment first revascularization strategy was associated with a better amputation-free survival, which was largely driven by fewer deaths in the best endovascular treatment group.
VOYAGER	NEJM 2020;382:1994-2004	**Title**: Rivaroxaban in Peripheral Artery Disease after Revascularization **Purpose**: To investigate the efficacy and safety of rivaroxaban for patients with PAD who have undergone lower extremity revascularization. **Methods**: Patients with PAD who had undergone revascularization were randomized to receive rivaroxaban plus Aspirin® or placebo plus Aspirin®. The primary efficacy outcome was a combination of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, or death. The primary safety outcome was major bleeding. **Results**: The 3-yr incidence of the primary efficacy outcome was 17.3% and 19.9% (hazard ratio, 0.85, 95% CI, 0.76 to 0.96; P=0.009) in the rivaroxaban and the placebo group, respectively. The primary safety outcome occurred in 2.65% and 1.87% (hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P=0.07) of the rivaroxaban and the placebo group, respectively. **Conclusions**: In patients with PAD, there was significantly lower mortality and morbidity in patients treated with ASA and rivaroxaban than those treated with ASA alone.
BEST-CLI	NEJM 2022;387:2305-2316	**Title**: Surgical or Endovascular Therapy for Chronic Limb-Threatening Ischemia **Purpose**: To investigate outcomes for surgical revascularization versus endovascular therapy as initial therapy for CLTI **Methods**: Patients with infrainguinal PAD and CLTI were categorized as with (cohort 1) or without (cohort 2) presence of a saphenous vein suitable as a bypass conduit and randomized to surgical revascularization or endovascular therapy within each cohort. The primary outcome was all-cause mortality or a composite of major adverse limb events (above-ankle amputation and major limb reinterventions) **Results**: For cohort 1, the primary outcome occurred for 42.6% and 57.4% in surgical revascularization and endovascular therapy groups, respectively (hazard ratio, 0.68; 95% CI, 0.59-0.79; P<0.0001). For cohort 2, the primary outcome occurred for 42.8% and 47.7% in surgical revascularization and endovascular therapy groups, respectively (hazard ratio, 0.79; 95% CI, 0.58-1.06; P=0.12). **Conclusions**: In CLTI patients with high-quality saphenous vein suitable as a bypass conduit, the incidence of mortality and limb-related morbidity was lower for surgical revascularization compared with endovascular therapy. In CLTI patients without a high-quality saphenous vein, outcomes were similar.

* For updated guidelines see the Society for Vascular Surgery's Clinical Practice Guidelines

Trial Name	Reference	Clinical Trial Details
AORTIC DISEASE		
EVAR1	NEJM 2010;362:1863-1871	**Title**: Endovascular vs. Open Repair of Abdominal Aortic Aneurysm **Purpose**: To evaluate the long-term outcome of EVAR compared with open repair of large aneurysms. **Methods**: Between 1999 to 2004, 1252 patients with large AAA (≥5.5 cm in diameter) were randomized to undergo either EVAR or open repair. Patients were followed for rates of death, graft-related complications, reinterventions, and resource use until end of 2009. **Results**: The 30-day operative mortality was 1.8% in the EVAR group and 4.3% in the open-repair group (odds ratio, 0.39; 95% CI, 0.18 to 0.87; P=0.02), but by the end of the study there was no significant difference in the rate of death from any cause (hazard ratio, 1.03; 95% CI, 0.86 to 1.23; P=0.72). The rates of graft-related complications and reinterventions were 3-4 times higher in the EVAR group. **Conclusions**: In patients with large AAAs, there was no significant difference in mortality in patients treated with open surgical repair and those treated with EVAR. Patients treated with EVAR had lower operative mortality but a higher incidence of graft-related complications, graft-related reinterventions, and healthcare costs.
IMPROVE	BMJ 2017;359:j4859	**Title**: Comparative Clinical Effectiveness and Cost Effectiveness of Endovascular Strategy vs. Open Repair for Ruptured Abdominal Aortic Aneurysm: 3-yr Results of the IMPROVE Randomised Trial **Purpose**: To compare the clinical outcomes and cost effectiveness of endovascular repair vs. open repair for patients with suspected ruptured AAA. **Methods**: 502 patients who underwent emergency repair for rupture were randomized to endovascular strategy or open repair. **Results**: Similar mortality between strategies by 90 days. There was lower mortality (48% vs. 56%), improved QALYs of 0.17 (95% confidence interval 0.00 to 0.33), and lower average costs of £2605 (95% confidence interval −£5966 to £702) in the endovascular strategy than the open repair group at 3 yr. **Conclusions**: At 3 yr, endovascular strategy for suspected AAA was associated with better outcomes and was more cost-effective than open repair.
CAROTID DISEASE		
NASCET	NEJM 1998;339:1415-1425	**Title**: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis **Purpose**: To investigate benefit of CEA in patients with symptomatic moderate carotid stenosis (<70%) **Methods**: Patients with focal symptoms of cerebral ischemia, within 180 days, ipsilateral to a moderate stenosis (<70%) were stratified by degree of stenosis (50-69% and <50%) and randomized to initial medical therapy versus initial CEA. The primary outcome was fatal or non-focal stroke ipsilateral to the index carotid stenosis. **Results**: For patients with 50-69% stenosis, 5 yr stroke rates were 15.7% and 22.2% in CEA and medical therapy groups (P=0.045). For patients with <50% stenosis, 5 yr stroke rate were 14.9% and 18.7% in the CEA and medical therapy groups (P=0.16) **Conclusions**: CEA reduced stroke risk in patients with symptomatic moderate carotid stenosis of 50-69%. Symptomatic patients with stenosis <50% did not benefit from CEA in comparison to medical therapy.
MATCH	Lancet 2004;364:331-337	**Title**: Aspirin® and Clopidogrel Compared with Clopidogrel Alone after Recent Ischaemic Stroke or Transient Ischaemic Attack in High-Risk Patients (MATCH): Randomised, Double-Blind, Placebo-Controlled Trial **Purpose**: To compare the benefits of adding ASA to clopidogrel vs. clopidogrel alone in prevention of vascular events with higher bleeding risk. **Methods**: 7599 patients with recent ischaemic stroke or TIA with vascular risk factor(s) that were already receiving clopidogrel were randomized to either ASA or placebo. The primary endpoint was the first occurrence of an event in the amalgamation of ischaemic stroke and related vascular complications. **Results**: 15.7% of patients in the ASA and clopidogrel group acquired primary endpoint, compared with 16.7% in the clopidogrel alone group (relative risk reduction 6.4%, (95% CI -4.6 to 16.3); absolute risk reduction 1% (-0.6 to 2.7)). Major and life-threatening bleedings were higher in the ASA and clopidogrel group compared to clopidogrel alone group but there was no difference in mortality. **Conclusions**: The addition of ASA to clopidogrel monotherapy in patients with prior ischemic stroke or TIA did not prevent recurrence of ischemic stroke, TIA, or related complications. Dual therapy was associated with a greater risk of major hemorrhage.
CREST	NEJM 2010;363:11-23	**Title**: Stenting vs. Endarterectomy for Treatment of Carotid-Artery Stenosis **Purpose**: To compare outcomes of CAS vs. CEA for patients with symptomatic or asymptomatic extracranial carotid artery stenosis. **Methods**: Patients with symptomatic or asymptomatic carotid stenosis were randomly assigned to CAS or CEA. The primary endpoint was a composite of stroke, myocardial infarction, or death from any cause during the perioperative period or any ipsilateral stroke in the following 4 yr. **Results**: The estimated 4-yr rates of the primary endpoint between the stenting group and the endarterectomy group were 7.2% and 6.8%, respectively (hazard ratio with stenting, 1.11; 95% confidence interval, 0.81 to 1.51; P=0.51), with no differential treatment effect based on symptomatic status (P=0.84). **Conclusions**: In patients with asymptomatic or symptomatic carotid artery stenosis, there were no significant differences in the combined risk of stroke, MI, or death between those who underwent CEA compared to those who underwent CAS. CEA was associated with a greater risk of MI, while CAS was associated with a greater risk of stroke in the postprocedural period.
VENOUS DISEASE		
ESCHAR1	Br J Surg 2005;92:291-297	**Title**: Randomized Clinical Trial of Compression Plus Surgery vs. Compression Alone in Chronic Venous Ulceration (ESCHAR Study)--Haemodynamic and Anatomical Changes **Purpose**: To evaluate the effects of superficial venous surgery and compression on legs with chronic venous ulceration. **Methods**: Patients with open or recently healed leg venous ulceration and saphenous reflux were randomized to either compression bandaging or superficial venous surgery plus compression. Venous refill times (VRTs) were calculated via photoplethysmography before treatment and at 1 yr later. **Results**: Out of 214 legs, 112 underwent compression bandaging and 102 underwent compression plus surgery. Saphenous surgery eliminated deep reflux in 10/ 22 legs with segmental deep reflux and 3/17 with total deep reflux. Median VRT increased from 10 to 15 seconds 1 yr later (P<0.001). **Conclusions**: Superficial venous surgery was effective in improving venous hemodynamics in patients with active or healed venous ulceration.
ESCHAR2	BMJ 2007;335:83	**Title**: Long Term Results of Compression Therapy Alone vs. Compression Plus Surgery in Chronic Venous Ulceration (ESCHAR): Randomised Controlled Trial **Purpose**: To evaluate whether superficial venous surgery in addition to compression bandaging prevents recurrent leg ulcers. **Methods**: Patients with open or recently healed leg ulcers and superficial venous reflux underwent either compression plus saphenous surgery or compression alone. Primary outcomes were ulcer healing and ulcer recurrence. **Results**: At three yr, ulcer healing rates were 93% for the compression plus surgery group and 89% for the compression alone group (P=0.73). At four yr, the rates of ulcer recurrence were 31% for the compression plus surgery group and 56% for the compression alone group (P<0.01). **Conclusions**: Superficial venous surgery and compression bandaging was effective in reducing the recurrence of venous ulcers compared to compression bandaging alone. Superficial venous surgery and compression bandaging did not reduce the healing time of venous ulcers compared to compression bandaging alone.

* For updated guidelines see the Society for Vascular Surgery's Clinical Practice Guidelines

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